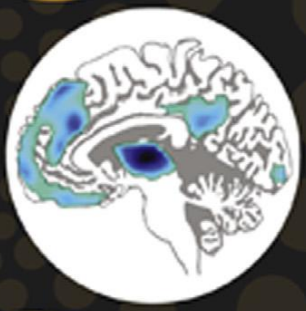
MODULATION OF SLEEP
BY OBESITY, DIABETES, AGE, AND DIET

Edited by Ronald Ross Watson



Modulation of Sleep by Obesity, Diabetes, Age, and Diet

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Edited by
Ronald Ross Watson
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Top right image on cover. One night of sleep deprivation is associated with reduced glucose metabolism (blue regions) within the brain (Thomas et al., 2000). Image file courtesy of Maria Thomas, with special thanks to Gregory Belenky of the Walter Reed Army Institute of Research and Henry Holcomb of Johns Hopkins University.

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Part I

Mechanisms of Sleep Deprivation and General Dietary Therapies

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Chapter 1

Diet, Age, and Sleep in Invertebrate Model Organisms

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INTRODUCTION

Diet, or the consumption of calories from the external environment, is an obligatory task of all metazoans. Yet the effects of the nutritional environment are not simply a binary fed/not-fed switch. The type and density of a nutrient source can have profound secondary effects. In a medical sense, the dietary components can be considered good or bad, either preventing or enhancing the onset of disease due to both caloric load and the presence of auxiliary chemicals that can be beneficial or toxic to cells and organ systems. However, from a broader perspective, the dietary composition can also provide essential information about the state of other attributes of the environment. These factors may have shaped the life history characteristics and behavioral responses of all organisms. For instance, the ripeness (amount of sugar) in fruits can provide seasonality information. The availability of food may also, directly or indirectly, signal the potential presence of predators, competitors, or mates.

In this chapter, I will attempt to summarize our current, albeit limited, understanding of the relationship between dietary factors, internal disease state, and sleep behavior in nonhuman animals, with a particular emphasis on the invertebrate model systems where we can leverage the power of genetics to move forward quickly. I encourage the reader to investigate several excellent recent reviews on the topic of sleep in less complicated organisms, particularly the genetics of sleep in *Caenorhabditis elegans* and *Drosophila* (Allada & Siegel, 2008; Cirelli, 2009; Crocker & Sehgal, 2010). Given the depth and quality of these reviews, I will attempt to instead focus specifically on the interconnected relationship between diet, sleep, and disease and highlight major areas where more work is desperately needed.

HOW DO WE KNOW THAT THE ANIMAL IS SLEEPING?

Before we launch into a discussion of how diet affects sleep in animals vastly different from ourselves, it is important to consider the characteristics of sleep. How do we know if an animal is sleeping? This remains a somewhat controversial issue. In 1913, Pieron proposed behavioral criteria that hold up today, including (1) a typical body posture and site, (2) a behavioral state of quiescence, (3) an elevated arousal threshold or reduced responsiveness to external stimuli, and (4) rapid state reversibility (to distinguish sleep from coma, injury, or death). Later researchers added the criteria of a homeostatic response to deprivation and responsiveness of the sleep periods to the circadian rhythm (Hendricks et al., 2000). In humans, electrophysiological correlates of sleep have become invaluable both to positively distinguish sleep from quiet wakefulness and to assess the organization of sleep stages throughout a period of sleep. However, one tricky aspect of this analysis is that occasionally most, but not all, signs of sleep will be present, leading to

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an ambiguous situation that becomes even more unclear as we assess the impact of environmental variables. As we shall see, rules are meant to be broken. For instance, the bullfrog *Rana catesbeiana* is notable for its daily pattern of rest with no change in arousal threshold (meeting criteria 1, 2, and 4) (Hobson, 1967). Marine mammals, particularly dolphins, show electrophysiological correlates of sleep but these are only unihemispheric (one side of the brain) and often associated with stereotyped circular motions of the body (meeting criteria 1 and 4) (Lyamin, Manger, Ridgway, Mukhametov, & Siegel, 2008). Similarly, three-toed sloths, some cats, and many birds show electrophysiological correlates of sleep during active waking, and sleep-deprived humans will also show evidence of "sleep" while behaviorally active (Campbell & Tobler, 1984). It seems clear that a completely rigid set of criteria cannot be applied to all animals and special consideration must be used when factoring in the relationship between sleep behavior and diet. Are all of these animals "truly" sleeping? Likely not. From the perspective of the reductionist, it may not matter or even be beneficial. The reductionist will study each piece of a complex behavior in the organism that is most amenable to study. This approach has been remarkably successful for seemingly intractable problems such as memory, neuronal excitability, and cell biology and is being increasingly applied to complex behaviors and social interactions.

DIFFERENT WAYS TO EVALUATE SLEEP

When considering an analysis of the environmental effects on sleep behavior, it is useful to consider not only the total daily sleep duration but also other characteristics of the sleep patterns, as these may impact the overall "quality" of the sleep experience. Some, but not all, of the characteristics may be affected by the dietary environment and disease state. These additional characteristics include the organization of the sleep behavior relative to the circadian day, the transition probability either into or out of sleep, the pattern of sleep states, and the number of sleep periods in the day (pure monophasic nighttime sleep appears to be a feature unique to simians). Furthermore, there are environmentally induced periods of sleep such as the rebound response to prior sleep deprivation and postprandial slowdowns that can share important characteristics with sleep. When considering the potential harm caused by disrupted sleep, there is both a concern regarding the overall long-term health status and the ability to safely complete waking tasks. For instance, a change in the probability of falling asleep (as is seen in narcolepsy) may not alter total daily sleep but would greatly impair safety and lead to loss of independence in a human. The organization of sleep states, such as slow wave and paradoxical sleep, within a given sleep period can also massively impact the quality of sleep. However, because evidence for the existence of sleep states in invertebrate model systems is scant (van Alphen, Yap, Kirszenblat, Kottler, & van Swinderen, 2013; van Swinderen, Nitz, & Greenspan, 2004), this chapter will focus on the analysis of behavioral patterns as indicators of the sleep–wake relationship.

One very useful broad generalization to consider when evaluating behavioral patterns is the reciprocal tradeoff between exploration and exploitation that characterizes behavior patterns and search strategies across a wide range of organisms. These alternating states of movement (exploration to seek resources) and relative inactivity (exploitation of the resources in a given area) are the foundation of reinforcement learning theory. The exploitation phase can comprise active feeding, mating, or sleeping. In all cases, there is a behavioral switch that turns off the exploration drive in order to promote dwelling, with sleeping being a potential extreme case of the dwelling phase where arousal is at a minimum. This relationship between exploration and exploitation is best characterized biochemically in terms of the "rover" and "sitter" phenotype in *Drosophila* larvae, where polymorphisms in a single gene, *foraging*, a cyclic guanosine monophosphate (cGMP)-dependent protein kinase, can tip the balance between the propensity for exploitation and exploration (Osborne et al., 1997). Given that activation of the cGMP signaling pathway through nitric oxide is a potent regulator of sleep behavior and cardiovascular health in mammals as well, it is likely that these basic concepts of the exploration/exploitation axis are retained through evolution and elaborated on to form the fundamentals of human sleep regulation.

CORRELATIONS BETWEEN ECOLOGICAL NICHE AND SLEEP BEHAVIOR

Before moving into the world of the model organisms, let us first consider the lessons of comparative biology. It is not surprising that the baseline sleep characteristics of an organism are shaped by its ecological niche. For instance, the challenges of an aquatic, terrestrial, or arborial domain will affect the tradeoffs that shape the stereotypical sleep patterns. Of particular relevance for this review, the correlation between typical diet and sleep duration is interesting. In general, there is a negative correlation between animal size and total sleep duration in mammals. However, if we look more closely, the effect of body size on sleep behavior has an interesting relationship with dietary consumption. For carnivores, there is no relationship between sleep duration and body size and sleep times are consistently greater than 8 h per day. However, there is an extreme negative correlation between body size and average daily sleep time in herbivores with the largest mammals coming in at under 4 h (Siegel, 2005). What is the reason for this diet-dependent difference in sleep behavior? Is stress a factor? While extremely interesting, these questions are unfortunately stubborn to definitively address in wild populations.

Instead, we will turn to the well-characterized genetic model organisms, where mechanistic hypotheses can be tested through a combination of genetic and environmental manipulations. Among the invertebrates, the leaders in providing mechanistic insight are *C. elegans* and *Drosophila melanogaster* due largely to the wealth of genetic tools and automated equipment for assessment. As we will see, *C. elegans* sleep is more recently characterized and therefore has been studied less deeply than that of *Drosophila*, which meets all of the criteria for the existence of true sleep.

The fields of behavioral genetics and neurobiology have recently been obsessed with mapping out the neural circuits responsible for behavioral states and making broad mechanistic interpretations about the way that organisms can process their environment. One reason for this enthusiasm with circuits is that evidence across widely divergent behavioral processes seems to indicate that the neuronal control of behavior and metabolism is largely a property derived from the action specific circuits rather than a property derived from the neurochemical state of the brain as a whole. Different molecules and neurotransmitters have widely different effects depending on the neurons involved. A classic example is the role of dopamine in *Drosophila* appetitive and aversive behavior depending on the site of activation (Burke et al., 2012; Liu, Placais, et al., 2012). Thus, both the "what" and the "where" are important for deeply understanding the mechanisms underlying the impact of environmental events on important physiological processes such as sleep.

EFFECTS OF DIET ON SLEEP

Two types of quiescent periods have been identified in *C. elegans* and purported to represent aspects of sleep. The first is lethargus, a period of behavioral quiescence and feeding cessation that marks the transitions between the larval stages (Raizen et al., 2008). The second is satiety-induced quiescence in the adult worm (You, Kim, Raizen, & Avery, 2008). In order to study this second state, worms are fasted and refed and a massively diminished movement profile is observed, coupled with the cessation of pharyngeal pumping behavior. This satiety-induced sleep state depends both on a prior period of fasting and on the quality of the food delivered after fasting, with a nutrient-dense food being required to induce the sleep-like state (Gallagher, Kim, Oldenbroek, Kerr, & You, 2013). Although the relationship between this satiety-sleep and true sleep is tenuous (there is no way to separate it from drowsiness), it offers a valuable opportunity to use this powerful genetic organism in order to understand the regulation of behavioral states by conserved molecular pathways. Furthermore, because the adult *C. elegans* has no other sleep-like state, postprandial sleep can be studied in perhaps its purest form. The initial forays into genetic dissection have returned a rough pathway for regulation. A recent report has implicated the ASI neurons in feeding-induced sleep (Gallagher et al., 2013) (Figure 1). The ASI neurons are a pair of bilaterally symmetric multifunctional sensory neurons that send ciliated dendrites into the amphid organs, a pair of small external openings near the worm's mouth, and then extend into the ring gland, a neuropil that serves as the worm's brain and primary secretory center (WormAtlas, 2002–2012). These neurons are activated by the transition from fasting to feeding, as measured by calcium imaging. Overall, the authors used standard genetic disruption in combination with genetic cell ablation using reconstituted caspases (Chelur & Chalfie, 2007) to assemble a putative mechanism. They found an interesting switching mechanism where the RIM and RIC neurons constitutively release an unknown hunger

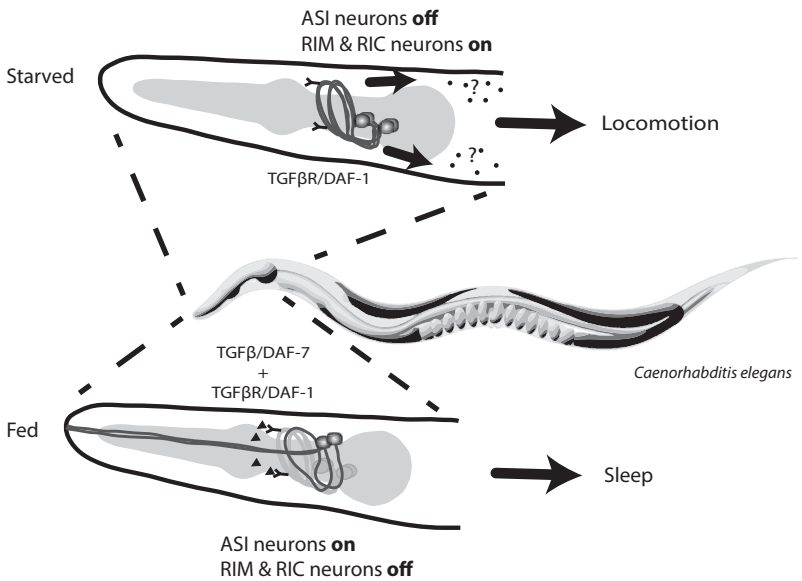

FIGURE 1 Regulation of *Caenorhabditis elegans* postprandial sleep. A close-up view of the head and pharynx area shows the RIM and RIC neurons on under starvation conditions (top) and the release of unknown locomotion-promoting signals into the circulation. When food becomes available, the ASI neurons activate (bottom) and release transforming growth factor (TGF)β/DAF-7, which binds the TGFβR/DAF-1 and promotes sleep-like quiescence.

signal in the absence of food. When food is perceived, the ASI neuron activates and releases transforming growth factor (TGF)β/DAF-7. This release suppresses the activity of the RIM and RIC neurons. cGMP generation and insulin release are also required, although the location of these signals in the neuronal circuit remains unclear (You et al., 2008). This simple circuit, when considered as a "wiring diagram," can provide basic insights into how an organism may receive and process environmental information. Furthermore, because the biochemical main players have vertebrate homologs that are regulators of sleep behavior, it is likely that this basic information will hold true across phyla. In particular, the relationship between TGFβ and sleep behavior in humans is not well established and awaits follow-up in a mammalian system. These initial forays have begun to map the regulation of sleep behavior and we can look forward to genetic screens that use simple behavioral assays to identify novel regulators of post-prandial sleep behavior that may also have vertebrate functional homologs.

The other major invertebrate model system for studying the effects of the environment on sleep is *D. melanogaster*. Here, we are particularly lucky because the genetics and neuroanatomy of circadian locomotor behavior are exceptionally well studied and the genetics of sleep are moving very rapidly. This organism is increasingly used to model human disease, and approximately 75% of known disease genes have homologs in *Drosophila* (Reiter, Potocki, Chien, Gribskov, & Bier, 2001). The relationship between food intake and sleep behavior is less clear, but various pieces of the puzzle are starting to come together (Figure 2). It is

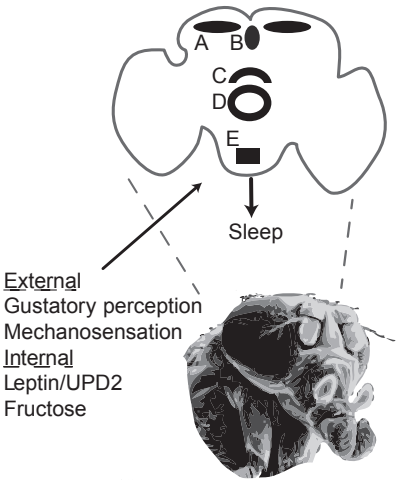

FIGURE 2 Regulation of nutrient status in *Drosophila*. Inputs from the external environment (gustatory perception, mechanoperception) and the internal environment (LEPTIN/UPD2, fructose) send information to the brain. This information is processed in distinct sites including (A) the dorsal cryptochrome-positive cells that respond to starvation, (B) the medial neurosecretory cells that secrete insulin-like peptides, (C) the fan-shaped body that regulates some aspects of sleep, (D) the ellipsoid body that contains hunger-regulatory cells, and (E) the subesophageal ganglion that processes gustatory information.

well known that food deprivation increases activity and promotes foraging in a range of animals, including *Drosophila* (Lee & Park, 2004). Keene et al. (2010) demonstrated that lack of food specifically impairs sleep behavior. They went on to identify a set of *cryptochrome*-positive neurons that had been previously implicated in circadian regulation of locomotion as being crucial for the regulation of sleep under nutrient stress conditions. This initial finding has opened the door for more detailed work on the mechanisms underlying tradeoffs between the need to seek food and the need to sleep. More recently, Erion, DiAngelo, Crocker, and Sehgal (2012) implicated octopamine (the invertebrate functional analog of norepinephrine) in a circuit regulating sleep deprivation in an interesting pathway that mechanistically separates fat storage (insulin dependent) and sleep behavior (insulin independent).

Our laboratory has also addressed the relationship between nutrient type and density and sleep behavior and found that modulating either sugar or yeast did not alter total sleep or its distribution between night and day but that sugar had a strong ability to regulate the length of sleep bouts through a mechanism involving gustatory perception and a second sensory-independent mechanism that was activated depending on the nutrient density of the food (Linford, Chan, & Pletcher, 2012). This result indicates that different nutrients have qualitatively different effects on sleep behavior and that animals can respond not only to the availability of food but also to its type and quality in order to regulate sleep behavior.

To date, there is no clear model in *Drosophila* for post-prandial sleep, similar to that in mammals and *C. elegans*. There have been additional reports of a very high protein diet either increasing or suppressing total daily sleep amount in *Drosophila* (Catterson et al., 2010; Katewa et al., 2012) as well as a related Queensland fruit fly (Fanson, Petterson, & Taylor, 2013). We have since investigated the situation in more detail and found that the high protein–induced sleep behavior is most pronounced immediately following feeding. Interestingly, these results may indicate that *Drosophila*, too, is a candidate for the study of post-prandial sleep.

While the relationship between dietary intake and sleep is only beginning to emerge in *Drosophila*, the neurogenetics of feeding and satiety regulation are being well-studied in other contexts and these may provide important insights into sleep behavior. Krashes et al. (2009) found a mechanism for the regulation of satiety-induced loss of feeding motivation that involves *Npf* (the insect version of neuropeptide Y) neuron activation in the absence of food, blocking an inhibitory signal from a population of dopaminergic neurons that feed into the mushroom body, a site of neuronal plasticity and memory storage. This relief from inhibition mechanism will undoubtedly inform a growing map of the relationship between external events and internal state.

Relatedly, Dus, Ai, and Suh (2013) recently found that a set of neurons in the central complex, the insect equivalent of the mammalian basal ganglion (Strausfeld & Hirth, 2013), directly modulates nutrient seeking when in a two-way choice environment with a nutritious and non-nutritious food. It is not clear where these neurons receive and send information, but the authors proposed that these may be direct glucose sensors.

Additional work has been conducted on the information flow into the brain that regulates feeding. It is likely that some or all of these sensors will regulate sleep as well. Input from the gustatory sensors on the proboscis (similar to the tongue) sends information to the subesophageal ganglion at the base of the brain where two sets of neurons have recently been shown to regulate food intake (Flood et al., 2013; Marella, Mann, & Scott, 2012). Furthermore, Mann, Gordon, and Scott (2013) provided strong insight into the neuronal control of behavioral states by noting that feeding is always performed while stationary and by identifying a pair of interneurons that block feeding in response to the mechanosensory stimuli of locomotion. Feeding is not only regulated by external sensors, and the mechanisms of internal nutrient status are beginning to be clarified. A *Drosophila* homolog of Leptin, *unpaired-2*, was recently established to signal from the fat body (fly adipose tissue) to the brain to alter insulin release (Rajan & Perrimon, 2012), and a novel mechanism for sensing fructose in the brain has been proposed (Miyamoto, Slone, Song, & Amrein, 2012). Together, this information on the regulation of information flow into and through the brain will allow us to carefully dissect the specific neurons and circuits that impinge on sleep behavior.

EFFECTS OF DISEASE AND AGE ON SLEEP

Very little is known about the effects of metabolic disease on sleep behavior in *Drosophila* or *C. elegans*, likely due to the early stage of research in characterizing their potential as disease models. In *Drosophila*, both genetic and dietary manipulation can lead to fat accumulation and an obesity-like state. Overabundance of either dietary sugar or fat has the potential to cause increased lipid storage, shortened life span, and defective cardiac function (Birse et al., 2010; Skorupa, Dervisefendic, Zwiener, & Pletcher, 2008). In the larval stage, dietary sugar produces a profound insulin resistance phenotype with an elevated hemolymph (insect blood) glucose that is extremely toxic to the organism (Musselman et al., 2011). In the adult, the effects of dietary sugar on insulin resistance are more subtle and potentially limited to females (Linford et al., 2012; Na et al., 2013). As for genetic models of altered fat accumulation, there is scant information on the relationship with sleep behavior to date. Thimgan, Suzuki, Seugnet, Gottschalk, and Shaw (2010) attempted to address this issue by altering lipid storage genes and determining the effect on sleep deprivation responses. Mutation of one fat storage gene, the perilipin homolog *Lsd2*, was able to block the negative effects of sleep loss, although it remains to be seen whether alterations in fat storage universally impact the response to sleep deprivation. Insulin production in the fly can be manipulated by disruption of the sites of production, termed medial neurosecretory cells, which are a set of neurons extending from the brain to release peptides and transmitters into the hemolymph near the heart. This cell cluster is thought to be homologous to the mammalian hypothalamus. These insulin-producing cells release three of the eight *Drosophila* insulin-like peptides. Ablation of the secretory cells by expression of the proapoptotic gene *reaper* leads to extended life span, altered size and fecundity, and reduced total daily sleep in a diet-dependent manner (Broughton et al., 2010). These and other models for diabetes and metabolic disease will likely help us dissociate the relationship between the disease state and the secondary characteristics, such as disrupted sleep behavior, that in humans may accelerate or exacerbate negative health.

The regulation of immunity is an active area of research in *Drosophila*. Insects have a primitive form of innate immunity that shares many commonalities with human innate immunity. The stress induced by pathogen load appears to suppress sleep (Shirasu-Hiza, Dionne, Pham, Ayres, & Schneider, 2007), similar to the effects of nutrient stress. Interestingly, when sleep loss is induced mechanically, immunity genes are induced (Zimmerman et al., 2006), indicating a reciprocal relationship between sleep and immune function and opening the possibility that immunity and sleep loss are strongly mechanistically related.

Finally, the effects of aging on sleep have also been examined. *Drosophila* is a well-established model for studying life span and the diseases of aging, and there are optimized protocols for achieving reproducible results. That said, the effects of age on sleep are not completely clear. Intriguingly, Koh, Evans, Hendricks, and Sehgal (2006) described age-associated sleep loss and an age-associated increase in the appearance of fragmented sleep (shorter, more frequent bouts of sleep), similar to the effects of age on sleep in humans. This age-associated sleep disruption has been seen by other groups but is not ubiquitous (Bushey, Hughes, Tononi, & Cirelli, 2010) and may depend on the food source (Yamazaki et al., 2012) or other aspects of the husbandry procedure. Koh et al. also noted that the effects of aging on sleep were similar to those of the oxidative stress inducer paraquat, and it may be that a prooxidant or an antioxidant feeding environment will affect the degradation of sleep in aging. This and other hypotheses related to the effects of aging and disease on sleep behavior have yet to be tested.

EFFECTS OF SLEEP ON FEEDING AND DISEASE

The effects of sleep on feeding and metabolic disease have primarily been studied in the context of restricting sleep through either mechanical or genetic methods. The data are sparse, but mechanical sleep restriction, even for a long duration, appears to have minimal effect on nutrient storage and fat accumulation in *Drosophila* (Harbison & Sehgal, 2009). This surprising conclusion was drawn from an experimental regimen of partial sleep restriction, so it is possible that in this model the flies were able to sufficiently recover sleep during the day. In another study using a sensitized background missing the circadian gene *cycle*, mechanical sleep deprivation caused rapid death, indicating that background genetics and health status may play a major role in the impacts of perturbed sleep (Shaw, Tononi, Greenspan, & Robinson, 2002). One important area that has not been addressed at all is the role of sleep perturbation on feeding behavior and/or the risk of metabolic disease, even though a simple model organism may be an excellent forum for such studies. In terms of aging, there is an interesting correlation between genetic perturbations that disrupt sleep and shortened life span for many (Cirelli et al., 2005; Koh et al., 2008) but not all (Bushey et al., 2010; Riemensperger et al., 2010) sleep-regulatory genes. Because there are no "pure" sleep genes, it is a bit difficult to interpret a negative result in this context. Even if sleep loss has a cost in terms of aging, any given intervention could have both positive and negative effects due to the pleiotropy of the molecules involved. Already, several reports have narrowed sleep regulation down to a single bilaterally symmetric pair of neurons (Liu, Liu, Kodama, Driscoll, & Wu, 2012). As the circuitry of sleep is increasingly well studied, the interventions will become more and more precise and it is likely that specific targeting of sleep regulation will be possible and will clarify the sleep–aging relationship.

SUMMARY

I have attempted to summarize the state of our knowledge on the interrelationship between sleep, diet, and age in the invertebrate model systems. Major areas of recent accomplishment in the field include recognition of the importance of controlling for nutrition, age, and disease state in studies of sleep, the emergence of initial characterization studies that reveal the nature of the relationship between sleep, diet, and disease, and the establishment of automated assays. Researchers have begun to identify small numbers of neurons and genes that are crucial for the environment–sleep relationship. With the increasing ease of manipulating the firing properties of single neurons in both *Drosophila* and *C. elegans*, I anticipate that we will see a much clearer map of the neural circuits underlying these sleep–diet and sleep–disease relationships in the next few years as well as new unexpected genes and biochemical pathways that come up from unbiased screens. There are also many more avenues to explore including the effects of social structures on the sleep–diet–disease relationship and the effects of motivation including rewarding and stressful environments. While these tiny model organisms may be very extremely different from ourselves at first glance, the organizing principles and biochemical pathways involved in behavioral decision-making likely shed novel insights on the fundamentals of basic human needs.

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Chapter 2

The Role of Sleep in the Control of Feeding Behavior

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INTRODUCTION

Sleep duration has been shown to be inversely related to obesity risk, and short sleepers are at increased risk of large weight gain over time (Patel & Hu, 2008). However, these epidemiological observations do not infer a causal role of short sleep duration (SSD) on obesity. Nevertheless, several explanations have been proposed to elucidate the role of SSD on obesity risk. One involves a reduction in physical activity due to increased fatigue whereas others involve increases in food intake, either because of increased time spent awake (opportunity to eat) or as a result of hormonal changes that trigger increased appetite/hunger (Penev, 2007). However, all scenarios propose a positive energy balance, either via reduced energy expenditure or increased energy intake, which would explain the association with obesity and large weight gain.

Several intervention studies have been performed in an attempt to determine whether SSD precedes the development of obesity and could be an explanatory factor in the etiology of obesity (Bosy-Westphal et al., 2008; Brondel, Romer, Nougues, Touyarou, & Davenne, 2010; Nedeltcheva et al., 2009; Schmid et al., 2009; St-Onge et al., 2011). Such studies have measured energy expenditure and energy intake during periods of sleep restriction compared with habitual sleep in normal sleepers (defined as sleeping 7–9 h/night). The amount of sleep permitted in those studies ranged from 4 to 6 h/night in sleep restriction studies to no sleep at all in sleep deprivation studies. The effects of sleep duration on components of energy balance (energy expenditure and energy intake) have been reviewed extensively by St-Onge (2013) and Penev (2012). In brief, on the basis of current literature, one would conclude that SSD leads to weight gain/obesity via increased food intake rather than as a result of a reduction in metabolic rate (energy expenditure). In fact, Shechter, Rising, Albu, and St-Onge (2013), Klingenberg et al. (2012), Markwald et al. (2013), have shown that sleep restriction increases 24-h energy expenditure measured in a metabolic chamber as a result of the extended time spent awake and the energetic cost associated with the wake state. Resting metabolic rate is not fundamentally altered by sleep restriction. However, the extent to which 24-h energy expenditure is increased with sleep restriction does not match the observed increase in energy intake associated with a similar degree of sleep restriction in clinical interventions. Additional and more extensive studies are needed to examine the effect of sleep restriction on voluntary physical activity. It is possible that restricting sleep leads to increased fatigue, which would prompt one to choose not to exercise or to do so at a lower intensity and thus energetic cost. However, this has not been verified in a clinical study. If this were the case, the reduction in energy expenditure associated with reduced voluntary physical activity would accentuate the state of positive energy balance that results when one is placed in a condition of sleep restriction relative to habitual sleep.

Although alterations in energy expenditure and energy intake are likely involved in the etiology linking SSD to obesity, the preponderance of evidence surrounds its effects

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on food intake. Thus, the purpose of this chapter is to review the effect of sleep restriction on food choice and the neurological pathways that guide these decisions.

EFFECT OF SLEEP RESTRICTION ON HUNGER AND FOOD INTAKE

It is now generally well accepted that sleep restriction leads to increased food intake. Spiegel, Tasali, Penev, and Van Cauter (2004) were among the first to ask participants about their feelings of hunger and appetite after a 2-day period of sleep restriction (4 h time in bed (TIB)) relative to extended sleep (10 h TIB). Participants provided hourly ratings, on a visual analog scale ranging from 0 to 10 cm, to questions such as "How hungry do you feel right now?" and "How much would you enjoy eating sweets, salty foods, starchy foods, fruits and fruit juices, vegetables, meat/poultry/fish/eggs, and dairy products?" The mean of all ratings for hunger was 24% higher after the two nights of sleep restriction relative to sleep extension, and the mean appetite rating for all categories of foods combined was 23% higher. Furthermore, the increase in appetite ratings for high-carbohydrate, calorie-dense foods, such as sweets and salty and starchy foods, after sleep restriction relative to sleep extension tended to be greater than that for other food categories (33–45% higher vs. 17–21% higher, respectively). However, some limitations of this study are worth noting. First, all participants were males and the sample size was small ($n = 12$). Also, participants were on constant intravenous glucose infusion as their sole source of calories throughout the study. The lack of food consumption may have amplified the effect of sleep restriction on hunger and appetite ratings. Moreover, these measurements were not followed by tests of ad libitum food consumption and, although subjective ratings are correlated with feeding behavior (Drapeau et al., 2005; Griffioen-Roose, Finlayson, Mars, Blundell, & de Graaf, 2010; Parker et al., 2004), it remained unknown whether participants would actually consume more of the foods they reported wanting on a visual analog scale. On the other hand, caloric intakes and energy source were very well controlled and identical under both conditions, removing an element of variability from their study.

Since then, studies have been undertaken to determine whether food intake would be altered by sleep restriction relative to habitual sleep. In an inpatient study, Nedeltcheva et al. (2009) assessed energy intakes over two periods of 14 days differing in TIB, either 8.5 or 5.5 h, in a crossover, randomized design. Overweight men and women participated in that study. When subjected to the restricted sleep period, participants ate an average of 300 kcal more than when they spent 8.5 h in bed. Food intake distribution over the day was such that snack energy intakes, but not meal energy intakes, differed between sleep periods. Specifically, energy intakes from snacks increased and the snacks chosen were higher in carbohydrates and lower in fat and protein during the period of sleep restriction relative to habitual sleep. Moreover, the rise in snack energy intakes was mostly observed in the evening/overnight period rather than during the daytime hours. A similar degree of overeating was also observed over a single test day performed after four nights of 9 or 4 h TIB (St-Onge et al., 2011). In that study, participants consumed approximately 300 kcal more during the short sleep period compared with the habitual sleep phase and this tended to be most pronounced in women, who specifically increased their intakes of fat and saturated fat in the SSD period. However, in that study, there was no effect of sleep restriction on late-night eating. Other studies have also reported increased energy intakes after periods of SSD (Bosy-Westphal et al., 2008; Brondel et al., 2010), although one study did not note this effect (Schmid et al., 2009). In that study, food intake was assessed the day after two nights of either 8- or 4-h TIB conditions.

The data by Nedeltcheva et al. (2009) showing increased evening/night intakes with SSD are in line with more recent information by Spaeth, Dinges, and Goel (2013) showing that restricting sleep leads to increased energy intakes at night. In that study, adults were randomized to five nights of 4- or 10-h TIB (sleep extension). Participants who were randomized to the sleep restriction protocol gained weight relative to those who were randomized to the sleep extension protocol. Energy intakes in the former group were higher than in the latter. There was no difference in the distribution of macronutrients in the diet between protocols. Also, in the sleep-restricted participants, meal number increased during the days when bedtimes were delayed to achieve sleep restriction compared with baseline (prerestriction days). In those participants, the distribution of energy intake throughout the day shifted over time. In particular, participants consumed fewer calories in the morning/early afternoon hours (8:00 a.m. to 3:00 p.m.) and more calories in the overnight period (10:00 p.m. to 4:00 a.m.).

NEUROENDOCRINE CONTROL OF FOOD INTAKE AND SLEEP DURATION

There has been much research to determine how sleep restriction affects food intake and the control of energy balance. Most studies have examined if sleep duration alters hormonal signals of hunger and satiety, mostly focusing on leptin and ghrelin. Although early studies have found that restricting sleep duration increases ghrelin (Benedict et al., 2011; Spiegel et al., 2004; Taheri, Lin, Austin, Young, & Mignot, 2004) and decreases leptin relative to habitual sleep (Spiegel et al., 2004; Taheri et al., 2004), this has not been universally observed. In fact, several studies have failed to show that restricting sleep leads to changes in leptin and ghrelin relative to habitual sleep (Nedeltcheva et al., 2009) whereas others have found opposite results—that sleep

restriction increases leptin (Bosy-Westphal et al., 2008; Omisade, Buxton, & Rusak, 2010; Pejovic et al., 2010; Simpson, Banks, & Dinges, 2010) and decreases ghrelin (Dzaja et al., 2004). The reasons for these discrepant results are not clear, and plausible explanations for these discrepancies have been the topic of a review of literature (St-Onge, 2013). Potential sex differences have been proposed, but only a limited number of studies examining the effect of sleep restriction on a food-intake-related mechanism included participants of both sexes. The largest study to date, by St-Onge, O'Keeffe, Roberts, Roy Choudhury, and Laferrere (2012), found that men, but not women, had increased ghrelin after three nights of sleep restriction relative to habitual sleep whereas women, but not men, had increases in glucagon-like peptide-1 concentrations under those same conditions. Leptin concentrations were not affected by sleep duration in men or women. This study is the only study to date to have explored sex differences in the hormonal response to sleep restriction and the first to assess the role of sleep duration on glucagon-like peptide-1 concentrations. These data illustrate potentially completely different mechanisms in which sleep restriction leads to increased food intake in men and women—one implicating increased hunger in men and one implicating reduced satiation in women.

Other potential explanations for the varied leptin/ghrelin results between studies include differences in the degree of sleep restriction and state of energy balance of the participants. It is known that leptin and ghrelin concentrations are affected by the body's internal energy status (i.e., they respond to alterations in energy balance such that corrections in energy intake and energy expenditure can be made to restore balance). If restricting sleep leads to overeating, as described above, then any difference in leptin and ghrelin observed between conditions of habitual and restricted sleep, performed in ad libitum feeding paradigms, could be in part explained by the differences in food intake.

Leptin and ghrelin are considered neuroendocrine hormones. These adipose and gastric-derived hormones produce hypothalamic signals to stop or start eating by initiating crosstalk between several important brain regions. These signals lead to changes in neuronal activity patterns that affect cognition, decision-making, and pleasure. Such processes then guide behavior. Orexins A and B, which are synthesized by lateral hypothalamic neurons, are also considered to provide a link between sleep–wake regulation and the neuroendocrine control of food intake (Hanlon & Van Cauter, 2011). Orexin neurons are active during wake and quiescent during sleep, and they activate neuropeptide Y neurons in the arcuate nucleus, leading to increased appetite. These neurons project to the dopaminergic ventrotegmental area and nucleus accumbens, which are involved in the hedonic control of food intake.

Thus, studies have been undertaken to examine the neuronal pathways involved in the control of food intake under various levels of sleep restriction. When sleep deprivation is enforced, the orexin system is overactive to maintain wakefulness against one's pressure to sleep, suggesting that neurons of the dopaminergic system would be stimulated to promote feeding behaviors (Hanlon & Van Cauter, 2011). Benedict et al. (2012) performed a functional magnetic resonance imaging (fMRI) study with 12 healthy, young, normal weight men in which scanning took place in the morning after a 7-h TIB sleep opportunity or total sleep deprivation (TSD). Participants consumed a standardized dinner (700 kcal) the night before and a light breakfast (125 kcal) approximately 15 min before scanning. During the scan, participants were shown pictures of low- and high-calorie foods, which they later rated as appetizing or not. TSD resulted in greater activation in the right anterior cingulate cortex in response to food images relative to sleep. Furthermore, participants rated more high-calorie food images as appetizing after a night of TSD compared with a night of sleep. The extent of the activation in the anterior cingulate cortex during TSD was significantly correlated with food ratings (appetizing). These data are particularly interesting because dopaminergic input via the mesocorticolimbic pathways is received by the anterior cingulate cortex and projected to the striatum, which is involved in the regulation of hunger motivation.

St-Onge, McReynolds, et al. (2012) also examined neuronal responses to food image stimuli after five nights of either 4- or 9-h TIB in normal weight, healthy men and women. Food intake was strictly controlled over the first 4 days but was ad libitum on the day immediately before the scan. Under conditions of sleep restriction, food stimuli led to increased activation of the putamen (thalamus), pulvinar (lentiform nucleus), orbitofrontal cortex, cingulate gyrus, precuneus, and inferior parietal lobule. When participants spent 9 h TIB, food images significantly activated the inferior parietal lobule, middle frontal gyrus, and hypothalamus. Finally, when sleep states were compared, food stimuli increased activation in the putamen, nucleus accumbens, thalamus, insula, orbitofrontal cortex, precentral gyrus, lentiform nucleus, precuneus, cuneus, and supramarginal gyrus to a greater extent in the sleep restriction phase relative to habitual sleep. Those regions are generally known for their association with emotional responses to stimuli and motivation and reward systems. Moreover, the authors observed that the neuronal responses to food stimuli in the restricted sleep state were similar to those observed in participants after a period of negative energy balance and weight loss (Rosenbaum, Kissileff, Mayer, Hirsch, & Leibel, 2010), and they proposed that restricting sleep may send neuronal signals analogous to energy deprivation, which would then prompt corrective actions to seek and obtain food. This would support the behavioral data obtained in that

study showing that participants eat approximately 300 kcal more in the sleep-restricted state than the sleep-replete state (St-Onge et al., 2011).

In the study by St-Onge, McReynolds, et al. (2012), foods were categorized as healthy or unhealthy. In an exploratory analysis of the data separated by food category, they further noted that unhealthy food stimuli specifically activated areas of the middle and superior frontal gyrus, right inferior frontal gyrus, left inferior parietal lobule, postcentral gyrus, and insula after sleep restriction whereas the inferior parietal lobule and medial temporal gyrus were activated after a period of habitual sleep (St-Onge, Wolfe, Sy, Shechter, & Hirsch, 2014). Moreover, relative to restricted sleep, habitual sleep selectively activated regions of the right thalamus, left precuneus, and middle cingulate gyrus in response to unhealthy relative to healthy foods. It was concluded that the activation of cognitive control mechanisms, when faced with appealing food stimuli, is not as well recruited after a period of restricted sleep, which may explain the apparent lack of restraint, or control, leading to increased intakes of snacks and higher fat foods in these conditions.

It is of interest that the inferior parietal lobule is activated by food stimuli in general and by unhealthy foods to a greater extent than healthy foods under periods of restricted and habitual sleep (St-Onge et al., 2014). De Havas, Parimal, Soon, and Chee (2012) have found that TSD reduces connectivity in the inferior parietal lobule of the default mode network, a network of brain regions that deactivates in response to externally driven tasks and activates in response to internally driven cognition tasks. They report the inferior parietal lobule as being involved in cognitive operations related to bodily awareness. This reduction in default-mode network inferior parietal lobule connectivity is observed after TSD. Our studies (St-Onge, McReynolds, et al., 2012; St-Onge et al., 2014) and the study of Benedict et al. (2012) were performed after acute severe sleep restriction. Perhaps either longer sustained periods of sleep restriction beyond five nights or TSD are needed to fully compromise this cognitive network.

The acute sleep restriction studies of Benedict et al. (2012), St-Onge, McReynolds, et al. (2012), and St-Onge et al. (2014) illustrate different neuronal networks that are involved in the response to food stimuli that implicate greater reward valuation after sleep restriction compared with habitual sleep as an explanation for increased food intake in this condition. Killgore et al. (2013) further examined whether self-perceived sleepiness, despite adequate, or normal, self-reported sleep duration, may be related to neuronal responses to food stimuli. Participants underwent fMRI scanning while viewing pictures of high- and low-calorie foods and rated the image on the basis of desire to eat ("How much would you like to eat this right now?"). Sleepiness scores on the Epworth Sleepiness Scale were positively correlated with appetite ratings, and this association tended to be stronger in women than in men. Furthermore, a single cluster in the ventral medial prefrontal cortex, an area important for evaluating the reward value of objects, regulating emotional responses, and controlling behavior, was also negatively correlated with sleepiness. Finally, in women, but not men, there was a negative correlation between the activation of the ventral medial prefrontal cortex and self-reported overeating ("Do you feel you eat more than you intend to?"). The authors concluded that daytime sleepiness was associated with a reduced activation of the ventral medial prefrontal cortex in response to high-calorie foods and that this was predictive of difficulty curtailing food intake, particularly in women. These results further support the notion that sex differences exist in food intake control responses to sleep restriction.

SLEEP RESTRICTION AND FOOD CHOICE

It is of interest to note that poor sleep quality is also associated with decision-making complacency and lower decision-making self-esteem in adolescents. Telzer, Fuligni, Lieberman, and Galvan (2013) found that hyperactivity of the insula occurred when processing positive stimuli in teens and that this was correlated with greater risk-taking likelihood, more decision-making complacency, and decision-making panic. They also found that reduced functional coupling of the insula and dorsolateral prefrontal cortex was associated with decision-making complacency and low decision-making self-esteem and vigilance, and that reduced functional coupling of the ventral striatum and dorsolateral prefrontal cortex was associated with increased likelihood of engaging in risk-taking behaviors and decision-making complacency. Therefore, if similar effects of poor sleep on decision-making and risk-taking behaviors are observed with SSD, one might expect that individuals with poor sleep quality or SSD would also make poor decisions with respect to their food choices.

Hogenkamp et al. (2013) explored the effects of sleep deprivation on a computer-based task to self-select portion sizes for a meal relative to a night of 8-h TIB. Young, normal-weight, healthy men underwent one night of 8-h TIB followed by 1 day of a fixed meal and food intake diet before being randomly allocated to the TSD or 8-h TIB night. The portion size task was performed at the same time the next morning and was followed by a controlled, 650-kcal breakfast and a second portion-size task. During the task, participants were shown pictures of seven different meal foods and six different snack foods, each presented in 51 different portion sizes ranging from 83 to 750 kcal. Self-reported hunger was greater after the night of TSD relative to the 8-h TIB night. Overall, portion sizes chosen on the computer task were larger after TSD than sleep and in the fasted versus the fed state. In the fasted state, food type did not affect portion size choice between TSD and sleep. However, after breakfast,

larger portions of snack foods, but not meal items, were chosen after TSD relative to sleep. The authors concluded that two independent mechanisms may be involved in the effect of sleep on feeding behavior: homeostatic and hedonic. However, food intake was not measured in this study, and it is unknown whether participants would have actually consumed what they reported they would in the portion task. Nevertheless, based on data from studies of food intake, one would expect that the results obtained by Hogenkamp et al. (2013) would be reflective of actual consumption patterns. One study has been conducted to investigate the association between the results of this task and actual and concluded that screen-based measures of portion-size selections were a valid method to assess energy intake in humans (Wilkinson et al., 2012).

Another study by the same group examined economic decision-making specific to food purchases after one night of TSD or one night of 8-h TIB (Chapman et al., 2013). Young, normal-weight healthy men underwent one night of 8-h sleep followed by a day of controlled food intake before undergoing either TSD or 8-h TIB in a crossover design. The next morning, participants ate a fixed 650-kcal breakfast at 8:00 a.m. and performed a mock supermarket task immediately after. For this task, participants were given approximately $50 (USD) to purchase from an array of 20 high-calorie and 20 low-calorie foods. Participants were aware of each food's price, energy density, and weight. In two subsequent trials, prices were manipulated such that high-calorie foods were either 25% cheaper or 25% more expensive than in the first trial. Participants were asked to spend as much of the money as possible and told that they were not permitted to make money savings. After the night of TSD, participants bought 9% more calories and 18% more grams of food than after the night of 8-h TIB. Making changes to the price of high-calorie foods did not alter the effect of TSD on purchasing behaviors. These data suggest that food purchasing may represent another mechanism through which a lack of sleep could promote food intake and put individuals at increased risk of large weight gain over time.

CONCLUSIONS

Studies to date have established that restricting sleep duration leads to alterations in food choices resulting in increased intakes of snacks and high-fat foods. Evidence suggests that SSD leads to changes in the hormonal regulation of appetite (although the exact mechanism remains to determined) and in the neuronal control of feeding behavior. It seems that, at least in individuals who do not regularly have SSD, restricting bedtimes leads to increased appetite and poor food choices. Leptin, ghrelin, and glucagon-like peptide-1 have been proposed to act at the hormonal level whereas the brain reward centers could be involved at the neuronal level. These imply that homeostatic and hedonistic controls of food intake could be affected by SSD. Future studies are needed to examine the contributions of each pathway to increased obesity and the effect of sex on this relationship.

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Chapter 3

Diagnosis and Treatment of Shift Work Disorder

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INTRODUCTION

Shift work disorder (SWD) is a prominent problem because approximately 16% of the workforce consists of shift workers (AASM, 2005; Drake, Roehrs, Richardson, Walsh, & Roth, 2004). SWD has been estimated in nearly 2–5% of the general population (AASM, 2005; Drake et al., 2004). Although most often reported in those who work nights or early morning shifts, SWD may be seen in anyone who works outside of the traditional 9:00–5:00 schedule, especially those who start work before 6:30 am or after 4:30 pm (AASM, 2005). More than 32% of night-shift workers meet the minimum criteria for SWD.[2] SWD develops out of a mismatch between the shift workers' innate circadian rhythm and their scheduled sleep–wake schedule. SWD, a type of circadian rhythm sleep disorder, typically occurs when a patient develops insomnia and/or excessive sleepiness as a result of shift work. Other symptoms can include headaches, lack of energy, weight gain, and trouble concentrating.

Patients with SWD commonly report poorer overall quality of life and are at risk for significant adverse events related to excessive sleepiness (Drake et al., 2004). Although cessation of shift work is curative for most who suffer from SWD, it is not always an option. Proper treatment is paramount for SWD given its significant prevalence within the workforce. This chapter will review the biologic basis for SWD, as well as the symptoms, diagnosis, and treatment (pharmacological and nonpharmacological).

CIRCADIAN RHYTHMS

The suprachiasmatic nucleus (SCN) contains the brain's master clock, which regulates circadian rhythms, self-maintaining rhythms that continue without the need of outside time cues. The SCN is located in the anterior hypothalamus (Moore & Eichler, 1972) and is the central pacemaker for the body. It is responsible for coordinating many biological processes to the outside environment as well as maintaining the temporal organization of these processes to one another. Photoreceptors in the eye transmit information about surrounding light levels through specialized cells that connect to the SCN through the retinohypothalamic tract.

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The circadian system describes physiologic variables including body temperature and blood pressure. These parameters can be described by a pattern having a specific period, phase, and amplitude. The circadian rhythm is approximately 24 h (Czeisler & Gooley, 2007). On the basis of currently available data, the most important factor for keeping a 24-h cycle appears to be the daily sunrise/sunset cycle (D'Alonzo & Krachman, 2000). The effect of light/dark factors on the circadian rhythm may be mediated by non-rod and non-cone photoreceptors in the eye. Other factors affecting circadian rhythm duration (including scheduled sleep and activity) have not been fully defined but appear to have trivial effect compared with the solar cycle (Aschoff, Fantranska, Giedke, et al., 1971; Baehr, Eastman, Revelle, et al., 2003; Czeisler, Allan, Strogatz, et al., 1986).

Sleep is modulated by balancing (1) the need for sleep with (2) the circadian rhythm. Within this balance, people experience a tendency to sleep during periods of decreasing body temperature; in contrast, body temperature increases upon wakening (Zisapel, 2001). The sleep cycle may be viewed as a physical representation of the circadian rhythm. Still, the likelihood of sleep is affected by acute sleep loss, sleep interruptions, and chronic lack of sleep (Czeisler & Gooley, 2007). Increasing homeostatic sleep drive will increase sleep propensity, which results in a neurobehavioral performance change. Sleep and wakefulness are disturbed if they occur out of sync with internal circadian time. This results in circadian misalignment—an example of which is when the circadian and homeostatic drives work to stimulate sleep at night but a shift worker must instead be awake during that time.

Various components of the sleep cycle are affected by the circadian rhythm. In one clinical trial, eight men lived in a setting free of time cues for over a month. During that time, the participants had scheduled sleep episodes in a 28-h rest–activity cycle (Dijik & Czeisler, 1995). Despite the imposed 28-h cycle, the internal circadian rhythm based on core body temperature was 24.1 h. Time to sleep initiation, sleep duration, wakefulness within scheduled sleep episodes, rapid eye movement (REM) and non-REM sleep, sleep spindle activity in non-REM sleep, and slow wave activity in non-REM sleep each vary significantly ($P < 0.0001$) with the circadian phase.

SYMPTOMS AND DIAGNOSIS OF SWD

SWD is characterized by excessive sleepiness during work hours coupled with insomnia during the time of sleep (AASM, 2005). There are many studies of subjective sleepiness in shift workers, with most reporting excessive sleepiness and dozing on the night shift, but no sleepiness during the times when sleep is desired during the day (D'Alonzo & Krachman, 2000).

In what seems like a common-sense approach, most shift workers revert to daytime activity and nighttime sleep on days off and vacations in an attempt to catch up on lost sleep and make time to socialize with others. This method, although well-intentioned, tends to lead to chronic disturbances in the sleep–wake cycle, thereby making it more difficult for the patient with SWD to adjust to their work schedule.

SWD may be associated with reduced alertness and performance capacity during the work shift. Irritability may also be present during the work shift, extending into the worker's personal time. This may, in part, be due to a lack of sleep, but it is also likely related to a conflict between social demands and the need to catch up on sleep.

The diagnosis of SWD is made using the American Academy of Sleep Medicine (AASM)'s International Classification of Sleep Disorders (ICSD)-2 diagnostic criteria (AASM, 2005). A diagnosis of SWD requires that, for at least 1 month, the patient suffers from insomnia during day/evening sleep and/or excessive sleepiness during work or commute to/from work. This must be associated with a recurring work schedule that overlaps with the usual time for sleep. A minimum of at least 7 days of sleep diaries with, ideally, additional actigraphy monitoring, is necessary to detail a circadian misalignment that results from shift work. Lastly, the sleep disturbance is not better explained by another sleep disorder; medical, neurologic, or mental disorder; the use of medication; or substance abuse. It is important to note that the formal diagnosis of SWD has rarely been used in clinical studies and requires further validation.

A thorough sleep and medical history with physical examination are necessary for appropriate diagnosis of SWD. The diagnosis of SWD can usually be made by history, although polysomnography may be necessary in severe or uncertain cases. Polysomnography should be obtained during the patient's usual, "shifted" sleep period and may show symptoms of insomnia including prolonged sleep latency, shortened total sleep time, or fragmentation of the sleep period due to frequent awakenings.

Several subjective questionnaires have been developed to assess excessive sleepiness. Although originally validated as a measurement of daytime sleepiness, these tools are commonly used to evaluate patients with excessive nighttime sleepiness when at work. The Epworth Sleepiness Scale is a self-administered questionnaire with eight questions about how likely subjects are to doze or fall asleep (Johns, 1991). Other popular measures of sleepiness include the Karolinska Sleepiness Scale, a nine-point evaluation ranging from "extremely alert" to "extremely sleepy-fighting sleep," as well as a 100-mm visual analog scale that ranges from "very sleepy" to "very alert" (Czeisler, Walsh, Roth, et al., 2005; Drake et al., 2004).

The most commonly used objective measure of daytime sleepiness is the multiple sleep latency test (MSLT), which

measures sleep latency under standardized conditions in the absence of external alerting factors (Littner, Kushida, Wise, et al., 2005; Mathis & Hess, 2009). MSLT results should be read within the context of the shift worker's clinical history and polysomnography. Actigraphy is an adjunct measure of sleep that measures limb movement; therefore, it may underestimate sleep onset latency due to inactivity before initiating electroencephalogram-defined sleep (Morgenthaler et al., 2007a).

The boundary between a normal and dysfunctional response to circadian stress of shift work remains unclear (Sack, Auckley, Auger, et al., 2007). Limited studies have investigated why some shift workers are more susceptible to SWD than others, and more research is needed to understand the mechanisms involved in developing SWD.

DIFFERENTIAL DIAGNOSIS OF SWD

Diagnosis of SWD requires exclusion of other causes of excessive sleepiness due to concomitant conditions such as obstructive sleep apnea, narcolepsy, another sleep disorder, a medical or neurologic disorder, a mental disorder, substance use, medication use, or insufficient sleep associated with conflicting daytime activities (AASM, 2005; Akerstedt & Wright, 2009). The symptoms of SWD may cause frustration and poor sleep hygiene and may lead to development of psychophysiologic insomnia and alcohol or drug dependency or abuse (AASM, 2005). Many circadian rhythm sleep disorders and medical conditions may mimic primary sleep disorders, including delayed sleep phase disorder, advanced sleep phase disorder, irregular sleep–wake rhythm, nonentrained type disorder, jet lag disorder, disorders due to metabolic conditions or to drug or substance use, and SWD.

CONSEQUENCES OF SWD

The relative risk of workplace injuries and accidents increases linearly from the morning shift through the night shift, with a 30.4% risk increase in the night shift compared with the morning shift (Folkard & Tucker, 2003). Relative risk increased over four consecutive night shifts, with a 36% greater risk on the fourth night compared with the first night. Further, data suggest that productivity is reduced significantly during night shifts. In one study, the work schedules of medical interns were altered to reduce work schedules and night shifts. Although this study reports a significant reduction in the number of serious medical errors, it provides only an indirect measure concerning the effects of sleep disturbance (Landrigan, Rothschild, Cronin, et al., 2004). In a prospective trial in which medical interns worked either a traditional schedule (30-h shift) or a modified schedule (16-h shifts with fewer night shifts), interns slept significantly less while on the traditional schedule and made significantly more errors (Lockley, Cronin, Evans, et al., 2004).

There is a correlation of shift work with cancer and heart disease. Several studies have indicated an increased risk for breast cancer in women who did not sleep during the natural peak in nocturnal melatonin (Davis, Mirick, & Stevens, 2001; Hansen, 2001). Risk of prostate cancer was significantly increased for rotating shift workers compared with day workers as reflected in the data from a large-scale prospective cohort study of male workers in Japan (Kubo, Ozasa, Mikami et al., 2006).

Data from one study evaluating effects of sleep disturbance on bowel function reported functional bowel disorders for 20% of nurses working day shift compared with 38% of nurses working a rotating shift (Zhen Lu, Ann Gwee, Yu Ho, et al., 2006). Sleep disturbance scores positively and significantly correlated with scores of dyspeptic symptom, anxiety, depression, well-being, fatigue, and somatic pain. Another study investigating the risk of developing heart disease as related to working night shifts found a linear trend toward an increased risk of heart disease with longer shift durations (Kawachi, Colditz, Stampfer, et al., 1995).

TREATMENT

Treatment guidelines for SWD have been developed by the AASM (Table 1; AASM, 2005) and include nonpharmacologic, nonprescription, and pharmacologic interventions. Treatments range from standard therapy of planned sleep/nap schedules to the use of hypnotics, stimulants, and alerting agents. Of note, the AASM guidelines do not include the most recent level of evidence for the U.S. Food and

TABLE 1 Management Strategy for SWD (Morgenthaler et al., 2007b)

Symptom-Based Management Strategies for SWD	
Alter circadian phase	• Timed bright light exposure • Modified sleep and work schedules • Exercise • Melatonin • Timed use of blue-blocking goggles
Increase nighttime alertness	• Modafinil • Armodafinil • Caffeine • Amphetamines • Planned naps • Bright light exposure
Decrease daytime insomnia	• Hypnotics • Melatonin • Proper sleep hygiene

Drug Administration (FDA)-approved agents modafinil and armodafinil.

A thorough, individualized approach is needed for the management of SWD due to varying shifts and sleep and social demands. The extent of the sleep disturbance and the effect of SWD on social and professional life need to be considered when developing a treatment plan. Intervention is aimed at encouraging circadian alignment, promoting sleep, and improving wakefulness at work.

Nonpharmacologic Interventions

Work schedule and lifestyle changes, exercise, and light enhancement may be effective in treating patients working shifts. However, these treatments have not been thoroughly studied in SWD, and more research is necessary to document any robust effectiveness in the SWD population. Nonetheless, the use of these methods is still recommended in a patient-specific paradigm.

Sleep Hygiene

Patients with SWD must be instructed in ways to ensure a sleep environment that is quiet, dark, and cool. All ambient light should be curtailed through methods such as blackout shades, sleep masks, black plastic on windows, or heavy drapes. Use of an air conditioner, fan, or even sleeping in the basement during warm days can ensure a cool environment. Noise can be blocked with ear plugs, a white noise machine, or placing carpets/rugs on outside floor surfaces to dampen the noise of family members walking around during the daytime. Family and friends need to understand the importance of protecting sleep time for the patient and all responsibilities, phone calls, and appointments should be tended to outside of the primary sleep period.

Day and Night Schedule Changes

Implementation of work schedule and lifestyle changes, exercise, and light enhancement in the workplace may benefit patients with SWD (Barger, Wright, Hughes, & Czeisler, 2004; Morgenthaler et al., 2007b; Schwartz & Roth, 2006; Youngstedt, 2005). Decreased performance and increased risk of accidents has been noted in multiple consecutive night shifts; shifts of 12 h or longer; early shifts starting before 7:00 am; weekly rotating shifts; backward rotations; complicated, split, and unpredictable schedules; lengthy commutes; consecutive/excessive weekend work; and night work with inadequate notice are all associated with an increased risk of accidents and injuries and decreased performance. If possible, modification of these schedules may be useful. Elimination of shifts that are longer than 12–16 h, limiting the number of consecutive night shifts, scheduling rotating workers to rotate clockwise, and screening workers for SWD and other sleep disorders are possible interventions. Educating workers about the risks of driving and working while sleep-deprived may help increase awareness of the risks associated with SWD.

Planned sleep schedules improve alertness and work performance and can decrease sleepiness during work hours (Czeisler, Moore-Ede, & Coleman, 1982; Morgenthaler et al., 2007b). Total sleep time can be increased by combining a primary, planned main sleep episode with scheduled naps. Reducing extended work hours combined with a nap before the night shift increases total daily sleep duration, ensuring sufficient sleep before work. Planned napping can improve alertness during shift work (Morgenthaler et al., 2007b). Preshift napping can increase vigilance and reaction times. Although data are limited in patients diagnosed with SWD, results are consistent between studies (Sack et al., 2007).

A steady sleep–wake schedule, 7 days a week, is ideal for adjusting to the night shift. However, such a schedule is admittedly difficult for many shift workers to follow, particularly on days off when the patient wants to spend time with family and friends and revert to a more "standard" nocturnal sleep schedule. If an extended, steady sleep period 7 days a week is impossible, then some patients find that keeping two 3- to 4-h sleep episodes during the day may be useful, with a more standard nighttime sleep pattern on days off. Another more recently studied strategy is to go to bed on nights off at a slightly later time than the patient would otherwise. For example, a patient would be instructed to go to bed on days off at 4:00 am and get up 8 h later, as opposed to keeping an 11:00 pm bedtime on off nights. This compromise in sleep pattern can help SWD patients adjust to their work schedule while also allowing for time to socialize on off days (Smith, Fogg, & Eastman, 2009). Several studies have investigated shift schedules that allow for better circadian adaptation. If possible, permanent night work may help to create a phase delay while the patient keeps daytime sleep even on days off. Rapid shifts (working one to two shifts in the same type in sequence) or clockwise rotation of shifts (morning-evening night-shift sequence) may be useful (Folkard, 2008; von Amelsvoort, Jansen, Swaen, et al., 2004).

Bright Light Exposure

Scheduled exposure to bright light and darkness can shift the circadian clock to align with a night-shift sleep schedule. Bright light exposure has been demonstrated to improve alertness, mood, and performance during the night shift (Burgess, Sharkey, & Eastman, 2002; Crowley, Lee, Tseng, et al., 2003; Drake & Wright, 2011; Morgenthaler et al., 2007b). Standard administration of bright light is either at the beginning of the shift for 3–6 continuous hours during the night shift or in 20-min blocks each hour (Boivin & James, 2002; Crowley et al., 2003). Of note, bright light exposure at night has been linked to an increased risk of cancer, thought to be related to suppressed melatonin levels

(Schernhammer & Schulmeister, 2004). More research is needed in this area because it is possible that other factors may also be involved in increased cancer risk, including shorter sleep duration, increased stress, and eating at an inappropriate circadian time.

Exercise

Epidemiologic studies have demonstrated that exercise can encourage sleep and affect the circadian system (Youngstedt, 2005). Although this has been true in epidemiologic research, experimental studies have failed to demonstrate a positive effect. However, Barger and colleagues elegantly demonstrated that daily exercise might facilitate phase delays of the circadian melatonin rhythm in very dim light (Barger et al., 2004). More research is necessary to investigate whether exercise is clinically beneficial for patients with SWD.

Nonprescription Interventions

Melatonin

Melatonin has not been well studied in clinical trials for patients with SWD.

Administration of exogenous melatonin has circadian phase shifting and hypnotic properties. Timed exogenous melatonin administration has demonstrated efficacy in promoting daytime sleep (Wyatt et al., 2006), but it does not increase nighttime alertness, performance, or MSLT scores (Sharkey, Fogg, & Eastman, 2001). Exogenous melatonin also displayed hypnotic properties only during sleep episodes that were out of phase with traditional sleep episodes, such as those of night-shift workers.

Caffeine

Caffeine enhances alertness in patients with SWD, lessening the power of the homeostatic sleep drive and improving alertness (Ker, Edwards, Felix, et al., 2010). Caffeine can significantly reduce the number of errors compared with placebo, improving cognitive formation, reasoning, perception, memory, orientation, and attention. Of note, many of these studies used simulated testing in healthy young subjects, and no trial participant had a formal diagnosis of SWD.

Dark Glasses

Although patients are advised to have light exposure during the night shift, it is equally important to avoid light exposure on the way home from work during the phase advance portion of the phase response curve. A potentially useful method of improving sleep in patients with SWD is the use of dark glasses to reduce exposure to bright light during a shift worker's commute home. Because the circadian clock is susceptible to the blue portion of the visible spectrum, several studies have found a positive adaptation to shift work solely through the use of dark sunglasses to block early morning light (Boivin & James, 2002; Crowley et al., 2003; Eastman, Stewart, Mahoney, et al., 1994; Sasseville, Benhaberou-Brun, Fontaine, et al., 2009).

Pharmacologic Interventions

FDA-Approved Agents

Currently, there are only two medications that have received FDA approval for improving wakefulness in patients with SWD: modafinil and armodafinil (Morgenthaler et al., 2007b). Modafinil was approved for use in SWD in January 2004, and armodafinil (the longer-lasting R-isomer of modafinil) was approved in 2007. Both medications are indicated for improving wakefulness in SWD patients with excessive sleepiness. No published, adequately designed, head-to-head clinical studies of armodafinil versus modafinil in SWD are available.

In a double-blind trial of modafinil for the treatment of excessive sleepiness in 209 patients with SWD, modafinil (200 mg) improved nighttime sleep latency and attention and decreased the symptoms of SWD. However, a portion of patients treated with modafinil (200 mg) continued to experience excessive sleepiness at the end of the study (Czeisler et al., 2005). Erman and Rosenberg completed a 12-week randomized, double-blind, placebo-controlled, multicenter study, demonstrating that treatment with 300 mg modafinil significantly improved patient functioning and health-related quality of life in 278 patients diagnosed with SWD (Erman & Rosenberg, 2007).

Several clinical trials have demonstrated efficacy of armodafinil for the treatment of excessive sleepiness in SWD. In a 12-week randomized controlled study, the efficacy of armodafinil (150 mg) was investigated during the night shift in 254 patients with excessive sleepiness associated with chronic SWD of moderate to greater severity (Czeisler, Walsh, Wesnes, et al., 2009). Nighttime sleepiness while working was significantly decreased, as measured by the MSLT. Armodafinil also improved ratings of attention, memory, sleepiness, and the severity of the SWD. Patients had reduced sleepiness during their commute home and had fewer mistakes, near-misses, or accidents during the night shift as reported in their patient diaries (Czeisler et al., 2009). In another study assessing long-term tolerability and efficacy of 50–250 mg armodafinil daily in 743 patients, of whom 113 had SWD, armodafinil improved clinical global impression of change efficacy assessments and was well tolerated (Black, Hull, Tiller, et al., 2010).

Controlled clinical trials have demonstrated that modafinil and armodafinil are well tolerated in patients with SWD (Czeisler et al., 2009; Roth, Schwartz, Hirshkowitz, et al., 2007). Adverse events are mild to moderate in severity, with the most common events being

headache, nasopharyngitis, nausea, anxiety, and insomnia. Rare but life-threatening rashes with both drugs have been reported in postmarketing studies (Nuvigil, 2007; Provigil, 2004). Changes from baseline in mean vital sign measurements (i.e., systolic and diastolic blood pressure and pulse rate) were slightly increased with armodafinil but not modafinil compared with placebo in some trials.

Hypnotics

Hypnotics such as zolpidem, eszopiclone, triazolam, and temazepam may be helpful in promoting daytime sleep in night-shift workers, but they typically do not improve nighttime alertness (Morgenthaler et al., 2007b). In addition, adverse effects must be monitored because these medications may create sedation during nighttime work performance (Morgenthaler et al., 2007b; Moon, Hindmarch, & Holland, 1990). Sleep-promoting agents have not been investigated in clinical trials with SWD patients, and more research is necessary to discern their utility.

Amphetamines

The effects of amphetamines (e.g., dextroamphetamine and methamphetamine) on focus and nighttime alertness have been studied in healthy volunteers and shift workers, but not patients with SWD (Comer, Hart, Ward, et al., 2001; Hart, Ward, Haney, et al., 2003) These medications should be used with caution to minimize the symptoms of excessive sleepiness (Schwartz, Roth, Hirshkowitz, et al., 2009). Methylphenidate is also approved for the treatment of narcolepsy and may be useful in SWD. These agents are schedule II medications and have a high potential for abuse and tolerance, with side effects including anxiety, agitation, anorexia, tachycardia, and elevated blood pressure. Some patients may experience hallucinations at higher doses.

SUMMARY

SWD is a common condition that often goes unrecognized and untreated among people performing shift work. Patients with SWD typically complain of insomnia and/or excessive sleepiness, have impaired work performance and productivity, and are at increased risk for motor vehicle accidents. The criteria for diagnosing SWD have been established by the AASM and published in the ICSD-2 and include demonstrating a shift-work schedule that interferes with the habitual sleep–wake pattern (AASM, 2005).

Employer and employee recognition of the potential health and productivity effects of shift work will lead to the institution of appropriate management recommendations. A patient-specific combination of behavioral, pharmacological, and nonprescription interventions proves to be most useful in SWD. Nonpharmacologic interventions may include sleep hygiene, sleep schedule changes, exercise, and bright light exposure. Over-the-counter melatonin or caffeine may also prove beneficial. Hypnotics may be indicated for improving daytime sleep. Modafinil and armodafinil are the only medications that are approved by the FDA in SWD to improve alertness while working. Appropriate recognition of and targeted therapy for SWD can improve sleep, performance, and quality of life for these patients.

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Chapter 4

Normal Sleep and Its Neurophysiological Regulation

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In today's 24-h society, with work going on 24 h/7 days per week, there seems to be less and less time for sufficient sleep. Although sleep is important for our physical and our psychological well-being, subjective sleep duration has been decreasing over the last 50 years, as pointed out in a review of Bixler (Bixler, 2009). The consequences of the lack of sleep cost our society dearly. Accidents related to sleep deprivation range from sleep-related traffic accidents (Horne & Reyner, 1999), train (Sussman & Coplen, 2000) and airplane crashes (Armentrout, Holland, O'Toole, & Ercoline, 2006), to serious work-related incidents (Åkerstedt, Fredlund, Gillberg, & Jansson, 2002). In 1994 (Leger, 1994) the annual costs in the United States of sleep-related road accidents were estimated as ranging from $43 to $56 billion per year.

The fatality rate and the number of incidents with serious injuries related to "sleepy driving" are comparable to those for accidents related to alcohol use. In a study in Australia and New Zealand, Williamson and Feyer (Williamson & Feyer, 2000) compared the relative effects of sleep deprivation and alcohol on driving performance. They found that people who drive after being awake for more than 17 h performed worse on the driving test than drivers with a blood alcohol level of 0.05%.

The dramatic consequences of sleep deprivation discussed above are probably to a large extent related to the attention problems created by lack of sleep (Lim & Dinges, 2010). However, sleep deprivation has a profound effect on many other aspects of health and cognition. For instance, sleep problems have been associated with immune suppression (Bryant, Trinder, & Curtis, 2004), diabetes (Beihl, Liese, & Haffner, 2009), and obesity (Taheri, Lin, Austin, Young, & Mignot, 2004). Furthermore, sleep is tightly linked to emotional state and emotional coping, and sleep problems increase the risk of developing affective disorders including depression and posttraumatic stress disorder (Spoormaker & Montgomery, 2008; Talamini, Bringmann, De Boer, & Hofman, 2013). Finally, sleep plays an important role in memory consolidation by strengthening neural connections (Peigneux et al., 2004; Talamini, Nieuwenhuis, Takashima, & Jensen, 2008).

NORMAL SLEEP PATTERN OVER THE NIGHT

Within sleep, two different states can be distinguished: rapid eye movement (REM) sleep and non-REM (NREM) sleep. These states alternate in a cyclical pattern (Carskadon & Dement, 2011, pp. 16–26) with a cycle duration of approximately 90 min. NREM sleep represents a continuum in which sleep gradually becomes deeper and the arousal thresholds gradually become higher. Brain waves, measured by electroencephalography, are described as more and more synchronized with deeper NREM sleep. REM sleep is characterized by more active brain wave activity, muscle atonia, and bursts of REMs.

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In the traditional literature, NREM sleep is subdivided in four stages (Rechtschaffen & Kales, 1968) representing sleep depth. Stages 1 and 2 are light sleep and the arousal threshold is low so that the sleeper can be easily awakened. Stages 3 and 4 represent deep sleep, where the awakening threshold is higher. In 2007, the American Academy for Sleep Medicine (AASM) launched a new system for the scoring of sleep and the events occurring during sleep (Iber, 2007). The main difference with the traditional Rechtschaffen and Kales scoring is that deep sleep is no longer subdivided in two stages. Rather, in the AASM scoring manual stages 3 and 4 are both scored as stage 3 (N3). Although various changes in the AASM scoring system are not without controversy, the system has been adopted now in many sleep clinics throughout the world. In this chapter, the AASM nomenclature for sleep stages is used.

The average sleep duration in an adult is 7.5 h during the week to 8.5 h on the weekend, but the variation in sleep duration is large (in general, between 6 and 9 h). Furthermore, cases of extreme short sleepers or long sleepers have been described in the literature for centuries. In addition to genetic factors, sleep duration may depend on environmental factors (e.g., evening activities forcing someone to go to bed at a later time or waking up by an alarm clock). For any individual, sleep duration is considered to be sufficient if the person's daytime performance is optimal.

Measurement of Sleep: Polysomnography

To describe the sleep pattern over the night, sleep is monitored by the measurement of brainwaves (electroencephalogram or EEG), eye movements (electrooculogram or EOG), and muscle tension of the chin (electromyogram or EMG). Customary electrode placements for the EEG are frontal (F4), central (C4), and occipital (O2) locations on the scalp according to the 10–20 system of electrode placement (Jasper, 1958). Electrical activity at these locations is measured in relation to a reference electrode placed on the mastoid behind the ear.

Additional information is needed to discriminate between the various sleep problems. Heart rate and cardiac events during sleep are generally measured with a single lead electrocardiogram (ECG). For the diagnosis of sleep-related breathing disorders or limb movement disorders during sleep, sensors for respiratory effort, respiratory flow, snoring, oxygen saturation, limb movements, and body position are used. The recording of the neurophysiological signals together with additional physiological signals during sleep is called *polysomnography*.

Sleep Stages

On the basis of the information from EEG, EOG, and EMG, a night of sleep is classified into sleep stages. Sleep generally starts with stage N1. Although during stage N1 the transition takes place between the wake state and the sleep state, it is difficult to pinpoint the exact start of sleep. During N1, the EEG shows a mixed pattern of alpha activity (8–12 Hz) and theta activity (4–7 Hz). Slow, rolling eye movements herald the beginning of sleep. The rolling eye movements disappear when sleep depth increases. In stage N2, sleep spindles and K-complexes appear, and the frequencies of the EEG are predominantly in the theta range. As stage N2 progresses, more and more delta waves (0.5–3 Hz) appear. When the percentage of delta waves increases to 20% or more, deep sleep is reached (stage N3). After this period of deep sleep, usually lasting approximately 20–30 min, light sleep returns. The first REM period, following after a short period of light sleep, is relatively short (~5 min). The EEG during REM sleep contains low-amplitude, mixed frequencies resembling the EEG during wakefulness. REMs, occurring in bursts, are visible in the EOG channels. In addition to the REMs, REM sleep is characterized by atonia of the skeletal muscles, which is visible in the electromyogram channel. During sleep, the autonomic nervous system changes its activity toward an increase in parasympathetic activity and a decrease in sympathetic activity. However, in REM sleep, there are intermittent surges of sympathetic activity, causing cardiovascular and respiratory irregularities, sometimes resulting in apneas. Although mental activity may occur during NREM sleep and REM sleep, the vividness and remarkable nature of dreaming is mainly associated with REM sleep.

Sleep Cycles

The average duration of a complete NREM-REM cycle is 90–110 min. After the end of the first REM sleep period, a new sleep cycle starts again with a period of light sleep, consisting mostly of N2. After some time, the slow delta waves of deep sleep reappear in the EEG. However, in general, the amount of N3 in the second sleep cycle is somewhat less than in the first sleep cycle. In the following sleep cycles, deep sleep may be absent altogether, leaving only light sleep and REM sleep.

Figure 1 shows the progression of sleep stages across the night, using the AASM classification nomenclature, of a young healthy adult. The cycling pattern of NREM sleep (stages N1, N2, and N3) and REM sleep is clearly visible, resulting in four or five sleep cycles with a duration of approximately 90 min each. The distribution of deep sleep (N3) and REM sleep across the night is asymmetrical: deep sleep is predominantly present in the first one third of the sleep episode, whereas the REM sleep episodes lengthen as the night progresses. In general, deep sleep shows a declining trend over the night.

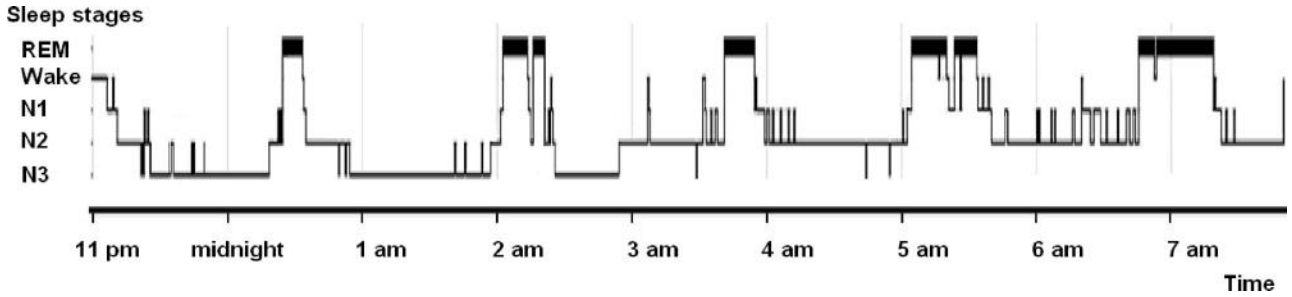

FIGURE 1 Sleep pattern over the night (AASM nomenclature).

During a night, the highest percentage of time is spent in light sleep (N1 and N2). In a young adult, the percentage of time in light sleep amounts to 50–60% of the night, whereas deep sleep (N3) amounts to approximately 15–20%. Finally, the time spent in REM sleep is 20–25%. These percentages change with age.

SLEEP IS REGULATED BY CIRCADIAN AND HOMEOSTATIC MECHANISMS

The timing of the sleep–wake rhythm is controlled by two processes: a circadian process, regulated by the biological clock, and homeostatic mechanisms or the need for sleep.

The circadian process is controlled by the biological clock, located in the suprachiasmatic nucleus (SCN) in the anterior hypothalamus. The existence of a circadian pacemaker in the hypothalamus was identified in rodents in 1972 (Moore & Eichler, 1972; Stephan & Zucker, 1972). Cells in the SCN generate a circadian output signal that drives most of our physiological and psychological rhythms. As a result of the influence of the central pacemaker in the SCN, our body rhythms fluctuate with an endogenous rhythm of approximately 24 h. In the absence of time information from the environment, the circadian rhythm deviates somewhat from the 24-h oscillation of the light/dark cycle: the rhythm is then said to be "free-running." The free-running period of the circadian rhythm in humans is slightly longer than 24 h (Czeisler & Wright, 1999), and every day our biological clock has to be reset to stay in synchrony with the outside world. The most important information used by the SCN to reset the clock is light. The retina has special ganglion cells, containing the photopigment melanopsin, that are sensitive to light (Gooley, Lu, Chou, Scammell, & Saper, 2001) and more specifically to blue light in the range of 460–480 nm (Lockley, Brainard, & Czeisler, 2003). The effect of light on the biological clock is dependent on the timing with respect to the endogenous SCN rhythm. Firstly in humans, as they are active during the daytime, the SCN is mostly sensitive to light during the subjective night, with little effect during the subjective day. Exposure to daylight in the second half of the night and early morning advances the rhythm of the clock, resulting in earlier sleep times. On the other hand, exposure to light in the evening and first half of the night delays the clock, resulting in later sleep times.

Individuals differ in various aspects of their circadian rhythms. One of the most well-known differences is the distinction between morning types (larks) and evening types (owls). The tendency of morning types to get up and go to bed at an earlier time than evening types is based on an endogenous difference in the timing of the circadian rhythm of their endogenous biological clock with respect to the light–dark cycle (Kerkhof & Van Dongen, 1996). Also, Duffy (Duffy, Rimmer, & Czeisler, 2001) found that morningness is associated with a shorter period of the intrinsic circadian rhythm of the biological clock. Chronotyping seems to be influenced by age (Roenneberg et al., 2007), with an increasing tendency to become morning types when we get older. In addition, more women than men are morning types (Adan & Natale, 2002).

The second regulatory process of the timings of sleeping and waking is the need for sleep, or sleep propensity. Sleep propensity depends strongly on the time we are awake. The longer we are awake, the more the sleep propensity will increase until finally a critical level is reached and we feel the need to sleep. Once we fall asleep, the need for sleep decreases until we wake up and the sleep propensity starts to build up again.

The circadian oscillations of the biological clock and the homeostatic regulation of sleep propensity together control the timing of falling asleep and waking up. The interaction between these two processes is described in the Two Process Model (Daan, Beersma, & Borbély, 1984). This model assumes that the circadian clock (process C) sets thresholds for the increasing and decreasing sleep propensity (process S). The upper threshold determines the time when the increase in sleep propensity is so high that the organism has to go to sleep and the sleep propensity starts to decrease. The lower threshold of the circadian process determines the end of sleep, when the sleep propensity starts to increase again.

SLEEP AND AGING

Sleep undergoes several changes across the lifespan. For one, the average sleep duration decreases from 16.5 h in 1-week-old babies to 8.5 h in 16-year-old adolescents to 7.5–8.5 h in adults. Sleep architecture also changes with age. In newborns, sleep consists of approximately 50% REM sleep. Moreover, deep sleep in infants does not show the declining trend throughout the night that is so apparent in adult sleep. Instead, deep sleep can also occur in a later part of the night (Bes, Schulz, Navelet, & Salzarulo, 1991). In fact, the sleep EEG in infants differs widely from that in adults, so much so that the sleep staging criteria applied in adults are not directly applicable to infants' sleep EEG. In fact, it is common practice to use the terms *active sleep* (somewhat similar to adult REM sleep) and *quiet sleep* (equivalent to adult NREM sleep) for the first 6–8 months of life. By the time daily napping disappears at approximately 4 years of age and the main sleep bout starts to concentrate in the night, the distribution of sleep stages across the night begins to resemble that of adult sleep. Another age-related difference is that young children sleep deeper than adults, with awakening thresholds that are approximately 10 dB higher than in adults.

In adolescents, some striking changes occur in the sleep pattern. Bedtimes are shifted progressively to later phases in the 24-h cycle while at the same time sleep duration is decreased. External factors, such as an increase in social activities and academic obligations, may play a role, but the preference for a later sleep phase in puberty seems to be mainly biologically driven (Carskadon, Vieira, & Acebo, 1993). During the school week, this phase delay in bedtimes together with the early school start times result in insufficient sleep. The adolescents try to make up for their sleep loss during the school week by sleeping in on the weekends.

Older people over 65 years of age often describe their sleep as lighter and less refreshing than when they were younger. Polysomnographic recordings show that the latency to sleep increases, that there are more awakenings, and that deep sleep decreases with age. In addition to more awakenings, there are also more arousals during sleep (i.e., short disturbances visible in the EEG without a real awakening). The decrease in deep sleep is influenced by gender: women may not show this decline (Bliwise, 2011, pp. 27–41). Overall, the duration of sleep decreases somewhat in people over 65 years of age, but when the increasing habit to nap in the afternoon is taken into account, there is not much difference with a younger age group. With increasing age, there is also a tendency to shift the bedtimes to an earlier time: This means that older persons tend toward becoming morning types.

Of note, the variability in sleep characteristics is very large in older adults. In addition to the normal age-dependent changes in sleep, there are also increasing effects of health-related factors. In old age, the predisposition to sleep problems such as apnea or restless legs increases in addition to the increase in general medical problems. This results in more disturbed sleep in older age.

NEUROPHYSIOLOGY OF SLEEP

History of Sleep Mechanisms

It was already in 1917 that the Austrian neurologist Von Economo described the cases of flu patients who either showed signs of extreme sleepiness or sleepiness with hyperactivity (Dickman, 2001). Because patients with either of these diseases showed changes in different parts of the midbrain, Von Economo concluded that the brainstem had to contain two regulatory systems: one for waking and one for sleep. In 1935, Bremer (Moruzzi, 1964) reported his experiments with cats in which he performed a transection above the brainstem at the level of the midbrain. In this "cerveau isolé" preparation, the cat showed clear signs of sleep in the EEG. Bremer concluded that the sleeping condition was "the result of the suppression, by the interruption of the corticopetal paths, of the steady flow of excitatory impulses." In other words, sleep was considered as a passive state in the absence of afferent stimulation from the brainstem. Further investigations in the involvement of the brainstem in vigilance led to the discovery of the "ascending reticular activating system" (ARAS) by Moruzzi and Magoun in 1949 (Moruzzi, 1964). Lesions in the rostral part of the pontine and mesencephalic tegmentum resulted in a sleeplike state with a synchronized EEG. On the other hand, stimulation of these cells resulted in EEG patterns showing all of the signs of a long-lasting activation. Moruzzi and Magoun hypothesized that these cells were able to activate the forebrain and, by doing so, maintain wakefulness. Later, as more cells were found contributing to the activation of the forebrain but lying outside of the core of the reticular formation, the name ARAS was changed to the ascending activating system (AAS). The various cell bodies in the AAS form a network with excitatory and inhibitory interactions.

Neural Control of Waking

A major part of the AAS is the cells in the laterodorsal tegmentum and pedunculopontine region of the brainstem (Figure 2(A)). These cholinergic cells project to the thalamus, the hypothalamus, the basal forebrain, and the prefrontal cortex. Another group of neurons that also express acetylcholine (ACH) is located in the nucleus basalis of Meynert in the forebrain itself and sends projections to the neocortex and the limbic system. Electric stimulation of these cholinergic systems causes activation and desynchronization of the cortical EEG, indicative of the waking state. The neurons in the laterodorsal tegmentum and pedunculopontine nuclei, as well as in the basal forebrain, show higher

firing rates in the wake state and during REM sleep than in NREM sleep (McGinty & Szymusiak, 2011, pp. 76–91).

In addition to the cholinergic pathways, there are other neurons, expressing norepinephrine, dopamine, serotonin, histamine, and orexin, that also contribute to the wake state. Norepinephrine is released from the locus coeruleus (Figure 2(A)), located in the pons. Another group of monoaminergic cells, containing serotonin, makes up the dorsal raphe nucleus (Figure 2(A)). Locus coeruleus and dorsal raphe neurons send widespread projections throughout the forebrain, thalamus, and cortex and play a role in maintaining wakefulness. Their firing rate is highest during wakefulness and decreases during NREM. In contrast to cholinergic neurons, these cell groups show little or no electrical discharge activity during REM sleep.

Similar variations in discharge rates are shown by histamine-releasing cells in the tuberomammillary nucleus, located in the caudolateral hypothalamus (McGinty & Szymusiak, 2011, pp. 76–91), and by dopamine-releasing cell groups in the ventral periaqueductal gray matter (Lu, Jhou, & Saper, 2006a). Neurons of the tuberomammillary nucleus send projections to the lateral thalamus, the basal forebrain, and the cerebral cortex. The ventral periaqueductal gray neurons project to the major parts of the brain that are involved in wakefulness.

An interesting, relatively recent finding is the involvement of the neurotransmitter orexin (or hypocretin), initially known for its relationship with feeding behavior, in the maintenance of the wake state. Orexin is produced exclusively in the lateral hypothalamus. The first notion that orexin might also play a role in sleep/wake regulation came from the discovery of the connection between orexin and narcolepsy in 1999 (Chemelli et al., 1999). The main symptom of narcolepsy is the occurrence of attacks of extreme sleepiness. A second symptom is cataplexy, with transient periods of extreme muscle weakness and loss of muscle tone, generally triggered by emotion. A cataplexic patient is unable to move, although he/she is fully conscious. Chemelli et al. (1999) reported that orexin knockout mice showed signs of narcolepsy similar to those observed in humans and dogs. They suggested that orexin was important for the regulation of sleep and wakefulness. However, the animal models did not fully translate to the case of human narcolepsy. For example, the group of Dement used an experimental breeding program for dogs and proved that narcolepsy could be inherited in dogs (Baker, Foutz, McNerney, Mitler, & Dement, 1982). Such a clear genetic factor seemed not to be present in humans. In homozygotic twins, one twin can have narcolepsy whereas the other twin is healthy (Hublin et al., 1994). However, in 2000, two different research groups (Peyron et al., 2000; Thannickal et al., 2000) found that a deficiency of orexin could also be detected in human narcolepsy patients.

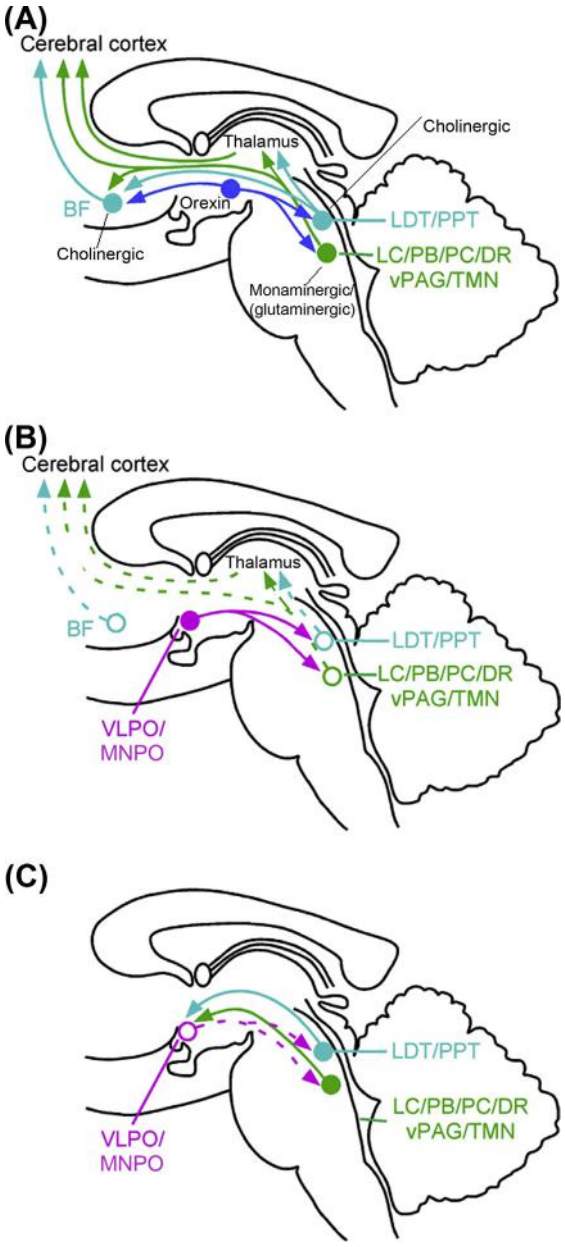

FIGURE 2 (A) In the upper brainstem (LDT/PPT), neural pathways maintaining wakefulness project to the thalamus (cholinergic) and to the hypothalamus, basal forebrain, and cerebral cortex (monoaminergic and possibly glutamatergic from the LC/PB/PC/DR/vPAG and TMN). This brainstem arousal system is reinforced by orexin-containing neurons in the lateral hypothalamus. Orexin neurons also project directly to the cerebral cortex and the basal forebrain. (B) The sleep system in the VLPO and the median preoptic nucleus (MnPO) inhibits (open circles) the ascending arousal systems to initiate sleep. (C) The ascending arousal system can, in turn, inhibit the sleep system. The mutual inhibition between the wake and sleep systems can be described as a flip-flop switch. DR, dorsal raphe nucleus; LC, locus coeruleus; LDT, laterodorsal tegmental nucleus; PB, parabrachial nucleus; PC, precoeruleus area; PPT, pedunculopontine tegmental nucleus; TMN, tuberomammillary nucleus; vPAG, ventral periaqueductal gray. *From Saper, Fuller, Pedersen, Lu, & Scammell (2010).*

Orexin-containing neurons are very active during wakefulness and send excitatory projections to the main parts of the AAS. Saper and his group concluded that orexin might be crucial to control the "gate" between wakefulness and sleep (Lu, Sherman, Devor, & Saper, 2006a; Saper, Chou, & Scammell, 2001).

Neural Control of NREM Sleep

During the transition between the wake state and sleeping, neurons in the ventrolateral preoptic nucleus (VLPO) in the hypothalamus increase their firing rate. They contain GABA (γ-aminobutyric acid) and galanin, two inhibitory neurotransmitters. VLPO neurons send projections to another hypothalamic area, the tuberomammillary nucleus, which, as we have seen in the previous section, is part of the AAS. The VLPO projections inhibit activity of the tuberomammillary nucleus. From neurons in the neighborhood of the VLPO (extended VPLO), other parts of the AAS, such as the locus coeruleus and the dorsal raphe, are also inhibited. The VLPO not only sends projections to components of the AAS, it also receives input from various regions that are involved in arousal. It has been shown that the VLPO neurons can themselves be inhibited by norepinephrine, serotonin, and ACH (Gallopin, Luppi, & Rambert, 2004; Gallopin et al., 2000). That means that the input from the various wake active neurons of the AAS, containing these neurotransmitters, inhibits the VLPO neurons. This mutual inhibitory activity between the VLPO and components of the AAS results in rapid switching between the wake state and the sleep state. Saper et al. (2001) referred to this behavior as a "flip-flop switch" in an analogy to an electronic switch (see Figure 2(C)). In the biological flip-flop mechanism, the mutual inhibitory action of the two sides of the switch results in only two possible self-reinforcing states. In this case, the two possible sides of the switch consist of the sleep state, caused by the increased firing rate of the VLPO neurons, and the wake state, resulting from increased firing of the AAS components. A deficit in either side of the switch would lead to instability of the switch, resulting in unstable fluctuations between the wake and the sleep state. Saper proposed that the orexin-containing neurons in the lateral hypothalamus could be important to stabilize the flip-flop switch. By reinforcing the wake maintaining activity in AAS regions and, thus, indirectly increasing the inhibition of VLPO neurons, orexin may prevent undesirable and faulty switches between the states of waking and sleeping (Saper, Fuller, Pedersen, Lu, & Scammell, 2010).

Neural Control of REM Sleep

As early as the 1960s it was observed that neurons in the brainstem, and more specifically in the pons, are important for the manifestation of REM sleep (Jouvet, 1962). This importance was corroborated by later research, which showed this regions' involvement in most, if not all, hallmarks of REM sleep. Indeed, neurons in the pontine reticular formation in the brainstem have been implicated in the production of REMs and muscle atonia. Moreover, activation of cholinergic cell groups in the pontomesencephalon induces the EEG desynchronization during REM sleep, which somewhat resembles the EEG wake state. These cholinergic cell groups are part of the midbrain reticular formation and of the more widespread AAS, which, as explained earlier, serve a broader role in the control of sleeping and waking.

As also explained above, REM sleep and NREM sleep alternate during the night, forming sleep cycles. Currently, there are two prevailing models of how such REM–NREM sleep alternations are regulated: the reciprocal interaction model (McCarley, 2007) and the flip/flop model (Lu et al., 2006b). The reciprocal interaction model assumes that REM-on and REM-off neurons interact with each other to control the cyclic alternation between REM and NREM sleep. The REM-on function is attributed to cholinergic neurons in the laterodorsal tegmental nucleus and the pedunculopontine tegmental nucleus, both located in the pontine mesencephalon, which fire just before and during REM sleep. Aminergic REM-off cells can be found in the locus coeruleus and the dorsal raphe nucleus. More REM-off cells, releasing histamine, are located in the tuberomammillary nucleus in the posterior hypothalamus. The REM-suppressing REM-off neurons typically stop or decrease their firing at the approach of REM sleep and remain silent throughout REM. McCarley (2007) proposes that the aminergic REM-off neurons have a "permissive role in REM sleep genesis" in the sense that their inhibition of the cholinergic REM-on neurons needs to be lifted to allow REM sleep occurrence. GABAergic neurons in the pons may also play a role in the control of REM sleep because increased activation of these neurons inhibits the REM-off neurons of the locus coeruleus and dorsal raphe and causes an increase in activation of the cholinergic REM-on neurons.

Lu et al. (2006b) have proposed another model in which the cyclic alternation between REM and NREM sleep is described as a flip-flop switch, as proposed earlier for wake–sleep transitions. However, the switch mechanism is now envisaged in the regions of the periaqueductal gray and pontine tegmentum. Two types of GABAergic neurons in these regions are viewed as REM-on and REM-off neurons: GABAergic neurons in the sublaterodorsal tegmental nucleus, firing during REM sleep, are the REM-on neurons, and GABAergic neurons in the ventrolateral periaqueductal gray and the lateral pontine tegmentum, which fire during NREM sleep, are implicated as REM-off neurons. Glutamatergic neurons are mixed in with GABAergic neurons in

REM-on and REM-off cell groups. The activities of REM-off and REM-on neurons inhibit each other, and this mutual inhibitory relation is responsible for the transitions between REM and NREM sleep. According to Lu, the cholinergic neurons in the pedunculopontine and laterodorsal tegmental nuclei and the monoaminergic neurons in the locus coeruleus and dorsal raphe nucleus are only modulating the basic flip-flop switch of REM sleep generation, but they are not part of the switch itself.

Thus, although considerable progress has been made since the first observations of Jouvet (1962), our understanding of REM sleep regulation is still far from complete.

SLEEP MECHANISMS AND THE CIRCADIAN CLOCK

The 24-h rhythm of sleeping and waking is regulated by the circadian clock in the SCN. Because sleep itself is regulated by other brain regions, some direct connections between the SCN in the anterior hypothalamus and the sleep regulatory system should be expected. However, hardly any direct projections from the SCN to regions that are known to be important for sleep/wake regulation can be found. The influence of the SCN on the sleep/wake regulatory system seems to involve multisynaptic pathways. The main projection of the SCN is the hippocampal subparaventricular zone. The subparaventricular zone sends projections to the dorsomedial nucleus of the hypothalamus and from there to the VLPO and the region in the lateral hypothalamus where orexin neurons can be found (Chou et al., 2003; Deurveilher & Semba, 2005). In this way, the necessary information from the biological clock can reach the regulatory systems of the sleep/wake systems to influence the timings of waking and sleeping.

CONCLUSION

Sleep is a complex phenomenon, and knowledge about its regulation is still incomplete. However, since the discovery of REMs in 1957, our knowledge of sleep has been exploding. The (electro)physiological description of sleep has increased our knowledge about normal and abnormal sleep patterns and has boosted the start of sleep medicine. Chronobiological findings about the biological clock in the SCN have revealed the relationship between the sleep/wake alternation and the regulation of circadian rhythms. From the more recent neurophysiological studies of sleep, we now know that the VLPO in the preoptic area of the hypothalamus is very important for the generation of NREM sleep. The mutual inhibition between the NREM sleep-generating neurons in the VLPO and the wake-generating neurons in the AAS in the brainstem controls the switching between sleep and waking. Orexin from the lateral hypothalamus may stabilize this switch.

The two prevailing models of the control of REM sleep both propose a mutually inhibitory interaction between REM-off and REM-on neurons. However, where the model of McCarley (2007) proposes an interaction between cholinergic and monoaminergic neurons in the pontine mesencephalon, the flip-flop model of Lu et al. (2006b) places this interaction between two groups of GABAergic neurons in the brainstem.

Concluding, neurophysiological studies have revealed that sleep is a complex and pluriform phenomenon governed by multiple interacting regulatory mechanisms. Thus, although sleep has relinquished some of its mystery, considerable questions remain to be unraveled in future studies.

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Chapter 5

The 1-2-3s of Pediatric Sleep Disorders

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Chapter Outline

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INTRODUCTION

From Sleeping Beauty to Sleepy the dwarf to Snow White, the topic of sleep presents itself more often than we think. Sleep is a major physiologic occurrence that is frequently a subject of conversation on a day-to-day basis. Sleep constitutes a major portion of time during a 24-h period, especially during the neonatal period into the toddler years. However, sleep is essential in all ages. It is a dynamic physiologic process that affects the physical, emotional, cognitive, and social development; however, the exact mechanisms that occur during sleep are not fully understood. Studies have shown that sleep abnormalities in children can lead to cognitive, behavioral, and social impairments (Chervin, Dillon, Bassetti, Ganoczy, et al., 1997; Mindell, Sadeh, Kwon, & Goh, 2013; Owens, 2001). Sleep abnormalities are often underestimated and underreported by caregivers.

Although sleep disorders are common in children, they can be challenging to the general practitioner. They may not only affect the child but also the caregiver. Barriers to successfully treating pediatric sleep disorders include social or cultural sleep practices such as bedtime routines, co-sleeping, sharing bedrooms with other family members, work/school schedules, feeding times, etc. (Mindell et al., 2013). Several studies have shown that despite increasing awareness about pediatric sleep medicine, significant knowledge gaps remain because of the lack of sleep education during medical training as well as recognition of the effect of sleep deprivation on a developing child (Faruqui, Khubchandani, Price, Bolyard, et al., 2011; Owens, 2001). Although some pediatric sleep disorders may overlap with adult sleep disorders, many pediatric sleep disorders are age dependent and can present as a spectrum from a child who is unable to fall asleep to a child who is too sleepy (Iglowstein, Jenni, Molinari, & Largo, 2003).

The focus of this chapter is for the general pediatrician as an easy-to-use guide to recognize and evaluate common pediatric sleep disorders in their every day clinical practice.

NORMAL SLEEP PHYSIOLOGY

Sleep is an active physiologic process that is regulated by a balance between the circadian rhythm and homeostasis. The circadian rhythm is the internal process that directs the timing and duration of the sleep–wake cycle (Crabtree & Williams, 2009). The circadian rhythm develops at approximately 10–12 weeks of age (Galland, Taylor, Elder, & Herbison, 2012). It is counterbalanced by the effect of the homeostatic drive during wakefulness. Homeostasis regulates the length and depth of sleep (Crabtree & Williams, 2009). During wakefulness, homeostasis accumulates progressively and promotes sleep.

Electroencephalography (EEG) activity can be identified in a fetus at approximately 24 weeks of gestation. Wakefulness and sleep can be differentiated at approximately 27–28 weeks postconceptional age. Sleep architecture has been identified as two distinct sleep states: rapid eye movement (REM) sleep and non-rapid eye movement (NREM)

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sleep. NREM sleep is divided into stage 1, stage 2, and stage 3–4 sleep. Stage 1 NREM sleep is the lightest stage of sleep that is often the initial stage of sleep in children and adults. It is distinguished from wakefulness by the absence of alpha rhythm, which is seen in the occipital EEG lead, and has a frequency of 8–13 Hz. Alpha rhythm activity is most prominent during wakefulness when the eyes are closed and attenuates with concentration or when the eyes are open. Recognition of this rhythm distinguishes between stages of wakefulness and sleep in adults. For children, the term *alpha rhythm* is replaced by the term *posterior dominant rhythm*. Stage 2 sleep typically follows stage 1 sleep and is characterized by K-complexes and spindles on EEG. Stages 3 and 4 represent the deeper stages of sleep and are also known as slow-wave sleep. It is predominant during the first third to half of the night in children. Because stages 3 and 4 have similar EEG characteristics, the American Academy of Sleep Medicine has combined both stages and renamed it as stage 3. REM sleep is characterized by a marked decrease in muscle tone and phasic rapid eye movements (Dement & Kleitman, 1957a, 1957b). The sleep cycle consists of REM sleep alternating with NREM sleep at 50–60-min intervals during the first year of age, which gradually increases to 75–90-min intervals at approximately 5–6 years of age (Crabtree & Williams, 2009).

During the newborn period, sleep consists of multiple brief sleep periods that are influenced by hunger and satiety (Crabtree & Williams, 2009). The amount of sleep they require is approximately 16–18 h over a 24-h period. Most of the day is spent sleeping with multiple nighttime awakenings through the night (Crabtree & Williams, 2009). Newborns and infants have a higher proportion of REM sleep compared with NREM sleep. Newborns typically enter REM sleep upon sleep onset. They gradually transition to NREM sleep upon sleep onset as the infant's nervous system matures (~6 months of age). The proportion of REM sleep to NREM sleep gradually decreases as the pattern of sleep shifts to the adult pattern of sleep (Crabtree & Williams, 2009; Iglowstein et al., 2003). By 6 months of age, sleep duration decreases to approximately 14 h (Iglowstein et al., 2003). By approximately 1 year of age, day sleeping begins to consolidate into one to two naps per day. Most children stop taking naps approximately 4 or 5 years of age in preparation for a full day of school (Crabtree & Williams, 2009). By childhood, sleep requirements gradually decrease to 10–11 h and then to 8–9 h during adolescence (Crabtree & Williams, 2009; Olds, Maher, Blunden, & Matricciani, 2010).

INSUFFICIENT SLEEP SYNDROME

The sleep requirement to maintain alertness and wakefulness for each age range varies as a neonate grows into adulthood. Insufficient sleep, or getting inadequate amounts of sleep relative to the child's sleep requirement over a prolonged period of time, has been shown to cause cognitive impairment, behavioral disturbances, and mood disorders (Hauri, 2005; Meltzer & Mindell, 2008). Adults manifest different symptoms when they are sleep deprived such as daytime sleepiness and problems with memory and concentration. Children may compensate for insufficient sleep by daytime sleepiness, excessive naps, or skipping favorite activities such as recess. Some children may demonstrate symptoms of attention-deficit hyperactivity disorder (ADHD) such as inattentiveness, impulsivity, hyperactivity, or the inability to focus on a single task (Maski & Kothari, 2013). Educating caregivers on the importance of sleep requirements will reduce subsequent adverse effects and can be easily treated by adjusting bedtime routines and sleep hygiene.

SLEEP HISTORY/PHYSICAL EXAMINATION

When evaluating for sleep disorders, the initial history from the caregiver can direct the diagnostic workup and plan. Sleep characteristics include how long it takes for the child to fall asleep and whether the child is able to maintain sleep through the night. If the child repeatedly wakes up, then questions should be directed to the possibilities of why: Was the child thirsty or hungry? Did the child need to use the bathroom? Does the child have nightmares or other fears? The number of hours of sleep achieved per sleep period will direct the physician on whether the child is sleep deprived. The number of naps during the day will also indicate whether the child is compensating for poor-quality sleep at night. Sleep deprivation or fragmented sleep have been shown to cause daytime symptoms such as inattentiveness, hyperactivity, irritability, labile mood, and excessive daytime sleepiness (Chervin et al., 1997; Crabtree & Williams, 2009). This is not optimal for a child because the expectation during the day is to perform well in school.

Events during sleep will also help guide the physician as to whether diagnostic workup is required. For example, noisy breathing, snoring, restless sleep, gasping, or choking for air may suggest sleep disordered breathing. Frequent jerking movements or leg movements may be a sign of seizures or periodic limb movement disorder (PLMD). Questions regarding sleepwalking, sleep talking, night terrors, etc., should lead the physician to ask questions regarding the child's safety during the episodes. In addition, the physician should also inquire about social situations that may contribute to the episodes, requiring a psychiatric or behavioral specialist intervention.

The child's bedroom environment should also undergo assessment during the sleep history. Books, television, toys, phones, and other electronics may prevent children from getting adequate amounts of sleep. The use of a nightlight may help alleviate fear of monsters or fear of the dark. Some children are sensitive to noise, which can interfere with initiating sleep. In addition, outlining where and when bedtime starts may provide insight to possible barriers such

as starting bedtime too early or too late to accommodate school/work schedules.

Furthermore, past medical history and physical examination can also be helpful in understanding why a child may have difficulty sleeping. Uncontrolled or chronic nasal congestion can contribute to snoring and frequent awakenings. Frequent coughing secondary to uncontrolled asthma is another reason for a child to have frequent awakenings and fragmented sleep. Cough variant asthma may be difficult to diagnose, especially if a child only has symptoms at night. Nocturnal coughing can also suggest irritation to the posterior pharynx from postnasal drip. The size of the oropharynx, the arrangement of the teeth (overbite, crowding), the presence of tonsillar hypertrophy, nasal turbinate hypertrophy, nasal septum deviation, micrognathia, retrognathia, short neck, or pectus deformities, and the overall muscle tone can direct the physician to suspect sleep disordered breathing.

DIAGNOSTIC TOOLS FOR PEDIATRIC SLEEP DISORDERS

In addition to the history and physical examination, sleep testing is helpful for the evaluation of pediatric sleep disorders. This includes overnight polysomnography (PSG), actigraphy, sleep logs, mean sleep latency test (MSLT), and sleep questionnaires.

The International Classification of Sleep Disorders-Second edition (ICSD-2) is a diagnostic and coding manual that provides a thorough review of sleep disorders and is available to all practitioners (Hauri, 2005). The manual includes essential features, diagnostic criteria, predisposing factors, pathophysiology, clinical findings, and differential diagnoses.

Overnight PSG is the most common diagnostic tool for most sleep medicine experts. The study includes EEG monitoring, electro-oculography to monitor eye movements, pulse oximetry, oronasal airflow, belts to determine abdominal and chest wall movements, chin electromyography to determine chin movements, leg electromyography to determine leg movements, exhaled end-tidal carbon dioxide monitoring, electrocardiography, snore microphone, and video recording. PSG is the gold standard to diagnose sleep disordered breathing and to titrate positive airway pressure in children (Aurora, Zak, Karippot, Lamm, et al., 2011). PSG is also indicated to diagnose sleep-related movement disorders, to confirm the diagnosis of an atypical or potentially injurious parasomnia, or to differentiate a parasomnia from nocturnal seizures (Aurora, Lamm, Zak, Kristo, et al., 2012).

Actigraphy is a device that is worn on the wrist that is able to discern states of wakefulness from sleep on the basis of muscle tone over a prolonged period of time. Actigraphy can be a valuable tool for use among pediatric patients, in which the common reliance on parental report alone may limit the range and accuracy of information about a child's sleep (Morgenthaler, Alessi, et al., 2007). Data regarding the child's sleep pattern from actigraphy are optimized when used with a sleep log.

There are several variations of sleep logs available by the American Academy of Sleep Medicine. Sleep logs are useful in identifying a specific sleep pattern from day to day. Because the caregiver reports a child's history, sleep logs can confirm the history when the sleep history is not clear.

An MSLT consists of a series of five 20-min nap opportunities that demonstrates an objective measurement of daytime sleepiness (Hauri, 2005). An MSLT can help identify the etiology of hypersomnia. A PSG is useful to exclude other major sleep disorders that could contribute to hypersomnia and to confirm that the child had sufficient sleep (at least 6 h) before the MSLT. Because children's sleep requirements vary with age, there are no current guidelines for sleep duration on the PSG preceding the MSLT in children, which can affect sleep latency times during the nap opportunities (Aurora et al., 2012).

When objective data are required and the caregiver's report is the only source of information, sleep questionnaires can be helpful. There are several sleep questionnaires available for health-care providers, such as the Pediatric Sleep Questionnaire , the BEARS questionnaire, and the Pediatric Daytime Sleepiness Scale (Chervin, Hedger, Dillon, & Pituch, 2000; Drake, Nickel, Burduvali, Roth, et al., 2003; Owens, 2005). Self-report sleep questionnaires, such as the School Sleep Habits Survey and Children's Sleep Habits Questionnaire can be helpful to screen for sleep disorders in specific age groups such adolescents and school-aged children, respectively (Moturi & Avis, 2010). There are currently no guidelines that recommend the best questionnaire for use in clinical pediatric practice.

BEHAVIORAL INSOMNIA OF CHILDHOOD

In general, the causes of insomnia in children are numerous. It can be related to a medical condition, pain, medication side effects, lack of a routine schedule, attention-seeking, or a combination of the aforementioned (Owens & Mindell, 2011). In contrast to adult insomnia, sleep issues are usually reported by the caregiver, especially if it delays sleep onset or requires prolonged intervention through the night, thus contributing to insufficient sleep for the caregiver (Morgenthaler, Owens, Alessi, Boehlecke, et al., 2006). There are two types of behavioral insomnia of childhood (BIC): sleep onset association type and limit setting type. BIC is more common in the preschool and older age group (Owens & Mindell, 2011). BIC occurs in 10–30% of the childhood population (Hauri, 2005).

BIC, sleep onset association type, is characterized by prolonged sleep onset as a result of not having the appropriate stimulation to fall asleep. Stimulation can include a special toy or blanket, rituals such as rocking in a chair or story time, person such as the caregiver, or environment such as co-sleeping or child's own room/crib. Without these associations, the child is unable to self-soothe and will present with prolonged sleep onset and frequent nighttime awakenings (Hauri, 2005; Owens & Mindell, 2011). Oftentimes, the child will cry or migrate into the caregiver's bedroom to receive the cues to resume sleep.

BIC, limit setting type, is characterized by the child delaying bedtime secondary to insufficient limits set by the caregiver. The child will stall bedtime by negotiating more time doing a particular activity such as watch television, temper tantrums, or attention-seeking behaviors leading to delayed sleep onset and insufficient sleep (Morgenthaler et al., 2006). There usually are no frequent nighttime awakenings (Owens & Mindell, 2011).

Both types of BIC can coexist; therefore, assessment of BIC is multifactorial. A thorough sleep history screening for medical, psychiatric, developmental disorders, performance difficulties in school, and associated burdens for the caregivers is helpful. Sleep schedule including nap times can provide insight on problems with regulating the sleep–wake cycle. It is also important to understand not only the caregiver's concerns regarding the child's sleep pattern but also the caregiver's expectation of what the child's sleep schedule should be.

Behavioral modification is the mainstay of therapy for both BIC types. The American Academy of Sleep Medicine recommends unmodified extinction, extinction with parental presence, graduated extinction, and preventive education as effective behavioral therapies (Morgenthaler et al., 2006). Unmodified extinction involves completely eliminating reinforcement such as parental attention when the child performs the unwanted behavior. The caregiver puts the child to bed at a designated time and does not pay attention to the child's resistance to bed. As a caregiver, this may be difficult to do; therefore, extinction with parental presence is more acceptable. The caregiver puts the child to bed at the designated bedtime but stays in the child's room. The caregiver still does not pay attention to the child's behavior. Over time, the caregiver eventually leaves the room with the child remaining in his or her own room. Graduated extinction involves the child attempting to self-soothe and fall asleep independently by the caregiver ignoring the child's crying or tantrums for a specific time period. That time period is gradually extended to longer time intervals to the point that the child is able to fall asleep without the caregiver. Parental education has also been found to be effective. This involves focus on positive sleep habits, maintaining a reasonable bedtime routine, and demonstrating self-soothing techniques for infants and toddlers (Morgenthaler et al., 2006; Owens & Mindell, 2011).

PARASOMNIAS

The ICSD-2 classifies parasomnias as a category of sleep disorders that involve undesirable behavior that accompanies sleep (Hauri, 2005). Parasomnias are benign and common. A Quebec prospective cohort study identified that 88% of children experience at least one parasomnia during their childhood (Petit, Touchette, Tremblay, Boivin, et al., 2007). The caregiver frequently reports them because they create concern and anxiety for the family. Common parasomnias in childhood include sleepwalking, sleep talking, sleep terrors, nightmares, confusional arousals, and sleep enuresis. Parasomnias can occur in NREM sleep, REM sleep, or both.

Sleepwalking, or somnambulism, consists of a series of complex behaviors that are initiated during arousals from slow-wave sleep (stages 3–4) and finish with the child walking with an altered state of consciousness. The prevalence of sleepwalking occurs in approximately 17% of children (Hauri, 2005). The episodes occur during the first third of the night, which consists of slow-wave sleep. The episodes often involve inappropriate behaviors such as urinating in the closet, moving furniture, climbing out of the window, etc. Most children cannot recall the episode in the morning. The predisposition to sleepwalking increases as the number of affected parents increase (Hauri, 2005). Sleepwalking spontaneously resolves as the child transitions into adolescence; however, sleepwalking can occur during adulthood.

Sleep terrors present with abrupt awakening with loud crying or screaming. The episodes are associated with autonomic discharge such as tachycardia, tachypnea, flushing of the skin, diaphoresis, mydriasis, and increased muscle tone. The child is usually unresponsive to external stimuli (Hauri, 2005). If they awaken during the episode, then the child appears confused and disoriented. Night terrors are common in children age 4–12 years and spontaneously resolve during adolescence (Guilleminault, Biol, Palombini, Pelayo, et al., 2003; Hauri, 2005; Sheldon, 2004). The prevalence of sleep terrors ranges between 1% and 6% (Hauri, 2005). Studies have shown those who experience night terrors also sleepwalk. Both parasomnias have been associated with separation anxiety (Petit et al., 2007).

Nightmares occur during REM sleep and are associated with an intense, frightening dream typically followed by a prolonged wake period. Nightmares have more of an emotional component as opposed to autonomic nervous system activation, which occurs with night terrors (Sheldon, 2004). They occur during the last third of the night and most children are able to recall the events of the dream. Treatment involves education and reassurance. Nightmares

typically resolve by 6 years of age. If the nightmares persist, then medical and/or psychological evaluation may be required (Hauri, 2005; Moturi & Avis, 2010).

Sleep talking, or somniloquy, consists of vocalizations that occur during NREM or REM sleep (Furet, Goodwin, & Quan, 2011). The vocalizations can range from simple, coherent speech to loud incoherent outbursts (Sheldon, 2004). It is the most frequent parasomnia; 50% of children have sleep talking reported by caregivers (Hauri, 2005; Petit et al., 2007). The child typically cannot recall sleep talking. Somniloquy has not been shown to be pathologic and resolves over time; however, it has been associated with other parasomnias such as sleepwalking, sleep terrors, and confusional arousals (Sheldon, 2004).

Confusional arousals consist of a state of confusion during or after an arousal from sleep. They occur during slow-wave sleep (stages 3–4) and occur during the first third of the night. The child may appear to be awake during some or most of a confusional arousal despite the diminished response to external stimuli (Hauri, 2005). Most episodes last approximately 5–15 min and occur in children age 3–13 years. Confusional arousals resolve as they age. Young children who have confusional arousals often go on to sleepwalk as an adolescent (Hauri, 2005).

REM-related sleep behavior disorder is most common in adults, but it has been seen in children. It is characterized by abnormal behavior during REM sleep that places the child at risk for injury (Hauri, 2005; Sheldon, 1998). PSG monitoring shows increased muscle tone in the chin, arm, and leg electromyograms during REM sleep. As a result, caregivers will report motor dream enactment that can be aggressive or violent, leading to injury to the child and/or to others. Medications such as clonazepam and melatonin have been used in small doses; however, treatment recommendations have been based on adult case series (Lloyd, Tippmann-Peikert, Slocumb, & Kotagal, 2012). Education on ensuring the child's safety should be strongly emphasized to the caregiver.

Sleep enuresis is another type of parasomnia that occurs in NREM and REM sleep. It is defined as recurrent involuntary voiding during sleep at least twice a week (Hauri, 2005; Moturi & Avis, 2010). There are two types of sleep enuresis: primary and secondary. Primary nocturnal enuresis refers to the child never remaining dry during sleep. It is more common in boys. Primary enuresis occurs in approximately 30% in four-year olds and approximately 10% in six-year-olds (Hauri, 2005). Secondary nocturnal enuresis refers to the child achieving voluntary control for at least 6 months and then begins bedwetting. Secondary nocturnal enuresis can occur as a result of a recent psychological stressor such as trauma or medical illness such as diabetes, urinary tract infection, or obstructive sleep apnea (OSA). Treatment options in conjunction with reassurance to the child include behavioral modification such as waking the child at specific times during the night to get the child to use the bathroom or using a urine alarm/bell, which addresses the difficulty children may have in waking in response to bladder sensations. Medications such as desmopressin have also been shown to be helpful (Kiddoo, 2012; Moturi & Avis, 2010).

For most parasomnias in general, treatment involves ensuring the safety of the child during the parasomnia as well avoiding insufficient sleep. Sleep deprivation can cause the events to become more frequent. Abrupt interruptions of the parasomnia by the caregiver may prolong the episode (Sheldon, 2004). In addition, comorbid conditions such as sleep disordered breathing, PLMD, and restless leg symptoms may contribute to developing chronic parasomnias. These conditions should be ruled out as part of the sleep evaluation (Guilleminault et al., 2003).

CIRCADIAN RHYTHM DISORDERS—DELAYED SLEEP PHASE SYNDROME

Delayed sleep phase syndrome is one of the most common types of circadian rhythm disorders. It is most commonly seen in adolescents. It is characterized by a physiological shift in sleep onset to later times of the night with eventual wake times occurring as late as in the afternoon. The sleep disruption leads to insomnia, excessive daytime sleepiness, or both (Hauri, 2005). The sleep pattern will show a shorter duration of sleep due to later bedtime as well as difficulty waking up early for school or work (Moturi & Avis, 2010; Sivertsen, Pallesen, Stormark, Boe, et al., 2013). Affected individuals will typically compensate for the shorter duration of sleep on the weekends by waking up later in the afternoon.

Actigraphy monitoring with a sleep log for at least 7 days will show a stable delay in the timing of sleep onset and wake time (Morgenthaler, Alessi, et al., 2007). PSG is not required, but if it is performed, the study is essentially normal for age. Those with delayed sleep phase syndrome have a lower sleep efficiency compared with adolescents and young adults who maintain a socially accepted bedtime and wake time (Sivertsen et al., 2013). As an end result, adolescents may have social or academic impairment (Hauri, 2005). Screening for illicit substance use as well as caffeine use may contribute to delayed bed times. In addition, undiagnosed depression and anxiety may precipitate delayed sleep onset as well as early morning awakenings.

Treatment includes behavioral approaches by decreasing bedtime by small increments of time until the desired bedtime is reached. Environmental adjustments such as exposure to dim light before bedtime, exposure to bright light upon awakening, and maintaining a consistent bedtime and wake time are also recommended (Morgenthaler et al., 2006). In addition, melatonin has been shown to reduce sleep onset latency, but it has not been shown to

increase the total sleep time or reduce daytime sleepiness (Morgenthaler, Lee-Chiong, et al., 2007).

RHYTHMIC MOVEMENT DISORDERS

In rhythmic movement disorders, a child reports simple, repetitive movements that disturb sleep. Two common pediatric rhythmic disorders include restless leg syndrome (RLS) and PLMD.

RLS, also known as Willis Ekborn disease, is a common neurologic movement disorder that causes an irresistible urge to move the legs. The essential clinical diagnostic criteria are as follows:

1. The urge to move the legs is described as an unpleasant or uncomfortable sensation that the child describes in his or her own words.
2. The urge to move the legs is enhanced by rest.
3. The urge to move the legs is accentuated in the evening and at night.
4. The urge to move the legs and the unpleasant sensation is partially or fully relieved by movement.

In children, the unpleasant sensation must be described in their own words in conjunction with fulfilling the diagnostic criteria of RLS. Oftentimes, it is helpful for the child to draw a picture of what they are feeling because some children have difficulty expressing their symptoms. There is often a positive family history of RLS.

Along with the history and physical examination, a serum ferritin may be helpful. It has been shown that low serum ferritin and ADHD symptoms may be associated with pediatric RLS (Picchietti & Picchietti, 2010). The pathophysiology of RLS involves abnormalities in cellular iron transport and of dopaminergic function. Iron acts a cofactor for tyrosine hydroxylase, which is an enzyme needed for dopamine synthesis. This is supported by improvement of symptoms with iron supplementation and dopaminergic agents (Picchietti & Picchietti, 2010). Factors that can contribute to worsening symptoms include insufficient sleep for age, pain, caffeine, alcohol, nicotine, and medications such as sedating antihistamines, serotonergic antidepressants, and neuroleptics.

Treatment for RLS includes lifestyle modifications including sufficient amounts of sleep, daily exercise, and avoiding precipitators such as caffeine, nicotine, or alcohol (Aukerman, Aukerman, Bayard, Tudiver, et al., 2006; Picchietti & Picchietti, 2010). Iron supplementation is recommended if the serum ferritin is less than 50 ng/mL. Medications to treat RLS in the pediatric population have not been approved by the U.S. Food and Drug Administration (Picchietti & Picchietti, 2010). However, in severe cases when there is severe sleep fragmentation, medications such as clonidine and gabapentin have been shown to improve RLS (Aukerman et al., 2006; Picchietti & Picchietti, 2010).

PERIODIC LIMB MOVEMENT DISORDER

Periodic limb movements (PLMs) are repetitive, involuntary movements that usually consist of extension of the great toe associated with flexion of the ankle, knee, and hip. PLMs are diagnosed by an overnight PSG that show of a series of four or more movements during any stage of sleep at intervals of 5–90 s that last 0.5–10 s (Hauri, 2005). If there is clinical sleep disturbance in addition to PLMs on a PSG, then the diagnosis of PLMD is established (Hauri, 2005; Picchietti & Picchietti, 2010).

PLMs may occur as an isolated condition or they may be associated with other sleep disorders (OSA, RLS, narcolepsy), neurologic disorders (multiple sclerosis, myopathies), medical conditions (renal failure, anemia), or medications such as antidepressants (selective serotonin reuptake inhibitors, tricyclic antidepressants, lithium). Although PLMD exists as a condition separate from RLS, many sleep experts consider PLMD as existing as a continuum with RLS. Currently, there are limited studies on therapeutic options for children; therefore, medications used to treat RLS have been used to treat PLMD (Aukerman et al., 2006; Picchietti & Picchietti, 2010).

SLEEP DISORDERED BREATHING

Sleep disordered breathing disorders is a group of disorders in which the respiratory pattern is altered during sleep. This includes central sleep apnea, primary sleep apnea of infancy, apnea of prematurity, central alveolar hypoventilation syndrome, and obstructive sleep apnea.

Central sleep apnea is defined as the absence of chest and/or abdominal movement associated with a cessation of airflow for more than 20 s. Alternatively, it can also be defined as lasting for more than two baseline respiratory breaths if it is associated with an arousal, an awakening, or an oxygen desaturation of at least 3% (Iber, 2007). Central sleep apnea can occur as an isolated condition or secondary to a medical condition such as brainstem lesions (e.g., Arnold-Chiari malformation), neurologic disorders (e.g., Joubert syndrome), Prader–Willi syndrome, or other sleep disorders such as sleep-related hypoventilation syndrome (Hauri, 2005; Kritzinger, Al-Saleh, & Narang, 2011).

Primary sleep apnea of infancy is characterized by prolonged central apneic events that are 20 s in duration or shorter than 20 s in duration and associated with obstructive or mixed apneic events and the presence of bradycardia, cyanosis, or generalized hypotonia (Hauri, 2005). It is recorded in infants 37 postgestational weeks of age or older. Apnea of prematurity has similar characteristics to primary apnea of infancy; however, it occurs in infants younger than 37 weeks postgestational age. The etiology of the condition is secondary to immaturity of the respiratory center. The severity of events improves as the infant matures. Therapy

mainly involves supportive care. However, medications such as caffeine may be helpful.

Congenital central hypoventilation syndrome (CCHS) is characterized by abnormal autonomic control of breathing during sleep. Age of onset is typically during the infancy period. Most cases of CCHS have been linked to the mutation of the homeobox gene *PHOX2B*. Transmission of the genetic mutation is autosomal dominant (Weese-Mayer, Berry Kravis, Ceccherini, Keens, et al., 2010). During wakefulness, the control of breathing is normal. However, during NREM and REM sleep, respirations are shallow and irregular. PSG may show severe hypercapnia and hypoxemia without apneas.

CCHS is a diagnosis of exclusion. Neurologic, cardiac, and metabolic disorders must be ruled out. In addition, other forms of central hypoventilation secondary to Arnold-Chiari malformation, trauma, central nervous system tumors, and obesity hypoventilation syndrome should be distinguished from CCHS (Muzumdar & Arens, 2008; Weese-Mayer et al., 2010). Conditions such as Hirshsprung's disease and neural crest tumors such as gangliomas and neuroblastomas have been associated with CCHS. A lifetime of mechanical-assisted ventilation is the mainstay of therapy, which can be delivered via tracheostomy tube, nasal mask via bilevel positive airway pressure, or negative pressure ventilation. Diaphragmatic pacing can also provide additional benefit (Weese-Mayer et al., 2010).

OSA is characterized by intermittent upper airway obstruction that disrupts normal ventilation during sleep. It is the result of narrowing of the upper airway and/or hypotonia of the upper airway (Hauri, 2005). Symptoms include restless sleep, snoring, noisy breathing or intermittent respiratory pauses during sleep, and/or daytime sleepiness. The child may sleep in unusual positions to maintain a patent airway such as in a seated position in effort to keep the neck hyperextended. Associated features with OSA include sinus arrhythmia, morning headaches, secondary enuresis, unexplained hypertension, and daytime hyperactivity (Hauri, 2005; Marcus, Brooks, Draper, Gozal, et al., 2012).

Physical examination may show obesity, tonsillar and/or adenoidal hypertrophy, or craniofacial abnormalities such as nasal septum deviation, retrognathia, micrognathia, macroglossia, midface hypoplasia, or hypotonia. Pectus deformities may develop as a result of paradoxical breathing due to having a compliant rib cage (Hauri, 2005). The gold standard to diagnose OSA in children is an overnight, attended PSG. The PSG demonstrates apneic episodes that may be associated with frequent arousals, increased respiratory effort, hypoxemia, and hypercarbia (Hauri, 2005; Iber, 2007).

Initial treatment for OSA in children is evaluation of the upper airway. In children, tonsilloadenoidal hypertrophy is the most common cause for OSA (Hauri, 2005; Marcus et al., 2012). Tonsilloadenoidectomies have been associated with improvements in sleep quality as well as daytime symptoms secondary to OSA (Marcus et al., 2012). Other risk factors associated with OSA include loud snoring, obesity, recurrent nasal congestion, recurrent wheezing, and family history of OSA (Redline, Tishler, Schluchter, Aylor, et al., 1999). For mild OSA, treatment after evaluation of the upper airway includes weight management, topical intranasal steroids, and antileukotriene medications. For moderate to severe OSA or for residual OSA after surgery, continuous positive airway pressure is recommended (Marcus et al., 2012; Verhulst, Franckx, Van Gaal, De Backer, et al., 2009).

HYPERSOMNIA/NARCOLEPSY

The ICSD-2 defines daytime sleepiness as the inability to stay awake or alert during expected wake periods. Hypersomnia refers to excessive daytime sleepiness that contributes to sleep fragmentation leading to insufficient sleep for at least 3 months. Hypersomnia is associated with increased daily sleep requirements without feeling refreshed despite having sufficient sleep opportunities. Other sleep disorders such as OSA or insufficient sleep should be ruled out as a cause of hypersomnia. In pediatrics, conditions of hypersomnia generally refer to narcolepsy, Kleine Levin syndrome, and menstrual-related hypersomnia.

There are three types of narcolepsy: narcolepsy with cataplexy, narcolepsy without cataplexy, and narcolepsy secondary to a medical condition. Narcolepsy with cataplexy is a chronic disorder of hypersomnia in which there are sudden onsets of sleep episodes or "sleep attacks" that are associated with cataplexy, sleep paralysis, and hypnogogic/hypnopompic hallucinations (Hauri, 2005). Cataplexy is the abrupt loss of skeletal muscle tone that is typically precipitated by intense emotion such as laughter or anger. During the cataplexic event, the person is conscious and may even anticipate the event. The cataplexy is usually bilateral and will last a few minutes. Sleep paralysis and hallucinations generally occur during the stages of transition between wake and sleep (Hauri, 2005; Viorritto, Kureshi, & Owens, 2012).

Current models show that narcolepsy is associated with the autoimmune destruction of hypocretin-secreting neurons in the hypothalamus (Mignot, 2004). Hypocretin is found in the perifornical area of the lateral hypothalamus, which is one of the principal neurotransmitters involved in the generation of wakefulness (Viorritto et al., 2012). Studies have shown low serum levels of hypocretin in the cerebrospinal fluid (<110 pg/mL) as a result of a decreased number of hypocretin-secreting neurons in narcoleptics with cataplexy (Hauri, 2005; Nakamura et al., 2011). Narcolepsy with cataplexy has a strong genetic association with human leukocyte antigen (HLA) subtypes DR2/DRB1*1501 and DQB1*0602. HLA typing can be helpful; however, it is not

the gold standard in establishing a diagnosis (Hauri, 2005; Nevsimalova, 2009).

Narcolepsy without cataplexy is defined as excessive daytime sleepiness for at least 3 months without the presence of cataplexy. Sleep paralysis and hallucinations may still be present. Unlike narcolepsy with cataplexy, a low level of hypocretin in the cerebrospinal fluid is only highly specific. In addition, a clear genetic association has not been identified. Narcolepsy due to a medical condition can occur in conjunction with brain tumors such as craniopharyngiomas, head trauma, demyelinating disease, central nervous system vascular malformations, and congenital disorders such as Niemann-Pick type C, Prader-Willi syndrome, Norrie's disease, Coffin-Lowry syndrome, and myotonic dystrophy (Hauri, 2005; Viorritto et al., 2012).

In addition to clinical history, an overnight PSG followed by a MSLT is the gold standard to establish the diagnosis of narcolepsy. The overnight PSG is performed to rule out the presence of primary sleep disorders such as sleep disordered breathing, PLMD, insufficient sleep syndrome, etc. An MSLT consists of a series of five 20-min nap opportunities that demonstrates an objective measurement of daytime sleepiness (Hauri, 2005; Viorritto et al., 2012). A mean sleep latency of less than or equal to 8 min and two or more sleep-onset REM periods on the MSLT supports the diagnosis of narcolepsy. Diagnostic criteria in children younger than 8 years of age are extrapolated from adult studies (Viorritto et al., 2012). Identifying low hypocretin levels in the cerebrospinal fluid as well as HLA typing may be helpful in children who are too young to undergo an MSLT.

There are currently no medications that are approved by the U.S. Food and Drug Administration for children with narcolepsy. The focus of therapy is directed on controlling the hypersomnia and cataplexy. Medications such as modafinil, sodium oxybate, venlafaxine, and methylphenidate have been commonly used (Aran, Einen, Lin, Plazzi, et al., 2010). Caregivers should receive education regarding adequate sleep hygiene and use of scheduled naps during the day to avoid sleep deprivation, which can exacerbate symptoms. Of particular importance, special attention to avoid driving when sleepy should be emphasized to teens and caregivers.

Kleine Levin syndrome is a condition of recurrent hypersomnia that is associated with symptoms that typically occur weeks or months apart (Hauri, 2005). The condition is more common in males. The age of onset is usually in early adolescence. The episodes of hypersomnia last for a few days to weeks and are preceded by headache or fatigue. Patients may sleep for as long as 16–18 h per day. Cognitive impairments such as confusion and hallucinations and behavioral impairments such as hypersexuality, binge eating, irritability, and aggressiveness have been reported. As a result, patients are at risk for social impairment and academic failure depending on the severity of the episodes of hypersomnia. In between the episodes, sleep and behavior is normal. There are no studies that demonstrate definitive treatment. Reassurance has been the mainstay of therapy (Mignot, 2012).

Menstrual-related hypersomnia is a condition of recurrent episodes of hypersomnia that occurs in association with the menstrual cycle (Hauri, 2005). It is not clear whether this is a subset type of Kleine Levin syndrome (Hauri, 2005; Mignot, 2012; Viorritto et al., 2012). Age of onset of the condition occurs within the first few months of menarche. Episodes usually last 1 week with resolution of symptoms at the time of menses. Oral contraceptives have helped prolong remission of episodes of hypersomnia.

SUMMARY

This review provides a brief and general overview of common pediatric sleep disorders that general pediatricians may see in their regular every day practice. Pediatric sleep disorders are common and may not be straightforward to diagnose, which can be a source of frustration for not only the caregiver but also the general pediatrician. As the importance of pediatric sleep medicine slowly unfolds to the general public, the goal of this review is to provide increased awareness to address sleep problems at routine well visits and allow general pediatricians to be familiar with common pediatric sleep disorders.

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Chapter 6

Sleep Disturbances, Body Mass Index, and Eating Behavior

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INTRODUCTION

There is increasing recognition that sleep and eating behaviors are related. The evidence for this association arises from clinical manifestations of sleep and eating disorders and from empirical findings using clinical and community samples.

The evidence that sleep might modulate eating comes from longitudinal and cross-sectional studies exploring the effects of sleep difficulties on eating disturbance/body mass index (BMI). These studies analyze the effect of sleep restriction on eating behaviors and weight/obesity, nocturnal sleep-related eating disorder (NSRED) and its comorbidity with eating disorders and obesity, and also sleep difficulties and eating behavior disturbance in subjects from the general population. Conversely, evidence on a link between eating disturbance/BMI and sleep difficulties also arises from longitudinal and cross-sectional studies exploring the modulation effect of eating behaviors/BMI on sleep disturbance in clinical settings of eating disorders (ED) patients, in subjects with night eating syndrome, in overweight/obese subjects and general population subjects. The association between eating and sleep disturbance might be bidirectional, as suggested by two studies with university students (Bos et al., 2013; Soares et al., 2013). The bidirectional association is not observed in respect to BMI. There is no overlap between eating disturbances and BMI with respect to their association with sleep disturbance. These results and those from other studies raise the question on eating disorders and weight overlapping regarding their association with sleep difficulties. We also explored psychological and neuroendocrine mechanisms that have been implicated in the relation between sleep and eating disturbances. With respect to psychological mechanisms, we paid special attention to the hypothesized mediation role

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of psychological arousal (Soares et al., 2013; Preedy, Patel, & Le, 2013), which was empirically explored in a sample of university students.

Clinical and research implications from these findings were examined.

STUDIES EXPLORING THE EFFECT OF SLEEP DIFFICULTIES ON THE MODULATION OF EATING DISTURBANCES/BMI

Short/Long Sleep Duration and Weight: Findings from Epidemiological, Population-Based Cohort Studies and Laboratorial Studies

Since the last part of the twentieth century, the trend of weight gain with a prevalence of increasing obesity and metabolic disease risk (e.g., type 2 diabetes) has accompanied nightly sleep decrease in the Western world (e.g., Killgore et al., 2013).

Several literature reviews of epidemiological studies on sleep restriction and weight link revealed that short (and, less frequently, long) sleep duration is associated with and is a risk factor for greater weight gain and obesity in children and adults (e.g., Cappuccio et al., 2008) or in specific age ranges throughout adulthood (Gangwisch, Malaspina, Boden-Albala, & Heymsfield, 2005). However, prospective cohort studies produced mixed findings, with some studies confirming that short as well as long sleep duration increased the risk for weight gain/obesity. Other studies found opposing results and suggested that only current short sleep was associated with obesity, and, therefore, sleep restriction was a correlate but not a predictor of weight gain/obesity (Anic, Titus-Ernstoff, Newcomb, Trentham-Dietz, & Egan, 2010; Lauderdale et al., 2009; Stranges et al., 2008).

Laboratory studies on behavioral and neuroendocrine mechanisms underlying sleep restriction and weight gain showed that sleep restriction induces metabolic disturbances (e.g., impaired glucose tolerance; increased plasma cortisol) and changes in the levels of appetite regulation hormones, specifically by increasing ghrelin (an orexigenic hormone released from the stomach) and decreasing leptine (an anorexigenic hormone released from adipocytes) (e.g., Spiegel, Tasali, Penev, & Van Cauter, 2004). These changes might promote hunger and affect the person's macronutrient preferences, eating behaviors, and patterns, leading to weight gain/obesity. Thus, experimental studies showed that sleep deprivation is associated with increased self-reported hunger and appetite (e.g., Spiegel et al., 2004), increased caloric intake (e.g., St-Onge et al., 2011), and greater consumption of and preference for caloric-dense and palatable foods, specifically for foods rich in carbohydrates (e.g., Nedeltcheva et al., 2009; Spiegel et al., 2004) and fats (e.g., St-Onge et al., 2011), including snacks (Nedeltcheva et al., 2009), sweets, salty foods, and starchy food (Spiegel et al., 2004).

Short sleep duration also might promote weight gain by increasing the frequency of meals and by a later circadian time of calorie consumption, such as consuming extra calories in the evening, at dinner, and during late night hours/early morning (e.g., Spaeth, Dinges, & Goel, 2013). Other factors such as health-related behaviors (physical inactivity and consumption of alcohol and tobacco), illness, use of medication, and psychological distress, which are associated with both short and long sleep duration, might contribute to weight increase/obesity (Theorell-Haglow, Berglund, Janson, & Lindberg, 2012).

Sleep Difficulties and Eating Behavior Disturbance/BMI in Convenience Samples of Subjects from the General Population

Two cross-sectional studies with two convenience samples of undergraduate students (Lopes et al., 2011; Soares et al., 2011) and one population based study with a retrospective design (Trace et al., 2012) suggested that current sleep difficulties are associated with current eating behavior disturbances and a lifetime history of eating disorders.

Soares et al. (2011), in a sample of university students of both genders, showed an association between sleep difficulties and eating behavior disturbance, particularly bulimic behaviors (BB). Both male and female insomniacs also revealed an odds ratio for BB higher than good sleepers. The association between sleep difficulties and social pressure to eat (SPE) is observable in males and the association between sleep difficulties and diet concerns (DC) is less consistent and only observable in females (Soares et al., 2011). BMI was correlated negatively with global sleep difficulties (Sleep Difficulties Index (SDI)), difficulties of initiating sleep (DIS), and insomnia symptoms, but it was not a significant predictor.

In university students of both genders, Lopes (2011) used three measures of subjective sleep restriction (sleep duration, sleep needs, and sleep deficit) and confirmed the association between lower sleep needs (<6 h sleep) and increased BMI in males but not in females. In a subsample of 303 females, eating behavior disturbances were also explored and female short sleepers (<6 h sleep) revealed higher levels of DC than females who usually slept more than 8 h, but no significant differences were found with respect to BMI between groups. The results also showed that sleep deficit was a predictor of eating behavior disturbances, particularly of BB. Although the associations between sleep duration and DC and between sleep deficit and global eating disturbance were also significant, they were mediated by self-reported psychological/mental health. With respect to BMI, although it was associated with

and predicted by high levels of global eating disturbances, BB, lower levels of SPE, and poor physical health, it is was not associated with sleep restriction in females.

A lifetime history of binge eating can be a risk factor for increasing prevalence of current sleep difficulties (not getting enough sleep, sleeping poorly, problems of falling asleep, feeling sleepy during work or free time, and disturbed sleep) in women from the general population, after controlling for lifetime history of depression and obesity status (Trace et al., 2012). After controlling for lifetime depression, only some sleep difficulties (early awakening and restless sleep) were not associated with binge and obesity status, which suggests that having a lifetime diagnosis of depression contributes to the association with some but not all sleep difficulties.

Nocturnal Sleep-Related Eating Disorder and Eating Disturbance/BMI

Other evidence that sleep is associated with disordered eating behavior comes from NSRED, which is characterized by a combination of sleep disturbances and abnormal eating at night. Nocturnal sleep-related eating disorder consists of a state of partial arousal from sleep, occurring within the first 3 h after sleep onset, followed by rapid episodes of ingestion of food (that can include eating in a sloppy manner or eating unusual combinations of food or inedible substances) described as out of control. Sometimes this arousal state is described as a confusional state or of half-awake or completely asleep, and in the following morning memory of the episode could be impaired (partial or total amnesia).

Nocturnal sleep-related eating disorder has also often been shown to be associated with lifetime and current eating disorder diagnosis (Schenck, Hurwitz, Bundlie, & Mahowald, 1991; Schenck, Hurwitz, O'Connor, & Mahowald, 1993) and with weight gain and a high prevalence of overweight/obesity (e.g., Schenck et al., 1991, 1993; Winkelman, 1998).

In subjects who were referred to sleep disorder clinics, the prevalence of NSRED was between 0.5% and 5% (Winkelman, Herzog, & Fava, 1999). In subjects with NSRED, anorexia nervosa with nocturnal bulimia was found in 10.5% (2 of 19) and nightly sleep-related binge eating in 84% by Schenck et al. (1993). A lifetime history of an ED was found in 10.5% and in 34.8% of patients (Schenck et al., 1991; Winkelman, 1998).

In subjects with eating disorders, NSRED was found in 16.7% of ED outpatients and 8.7% of ED inpatients (Winkelman et al., 1999). Gupta (1991) observed that 31% of bulimic females had NSRED with partial amnesia two or three times per month.

Studies on the prevalence of NSRED in undergraduate students showed rates between 0.6% (Goldin & Rosen, 1997) and 4.7% (Winkelman et al., 1999).

STUDIES EXPLORING EATING BEHAVIOR DISTURBANCES/BMI EFFECT ON MODULATION OF SLEEP DIFFICULTIES

Studies in ED patients, patients with night eating syndrome (NES), and subjects from the general population suggested that sleep might be modulated by disordered eating/BMI. Body mass index is considered a proxy of eating disorders; it is included in ED diagnostic criteria and BMI cutoffs are used to define overweight/obesity (Figure 1).

Eating Disorders and Sleep

Eating disorders, namely anorexia nervosa (AN), bulimia nervosa (BN), and binge eating disorder (BED) (APA, 2013), are characterized by severe eating behavior disturbance and nutritional deviance.

Core features of AN are (1) persistent restriction of energy intake and maintenance of excessively low body weight considering the age, height, sex, developmental trajectory, and physical health; (2) intense fear of gaining weight or becoming fat or persistent behavior that interferes with weight gain (APA, 2013; ICD-10, 1992); and (3) disturbance in self-perception of weight or shape and undue influence of body weight or shape on self-evaluation. ICD-10 also includes the loss of sexual interest or potency in men and amenorrhea in post-menarche women (ICD-10, 1992) Amenorrhea is part of DSM-IV-TR (APA, 2002) AN criterion but is excluded from DSM5 (APA, 2013).

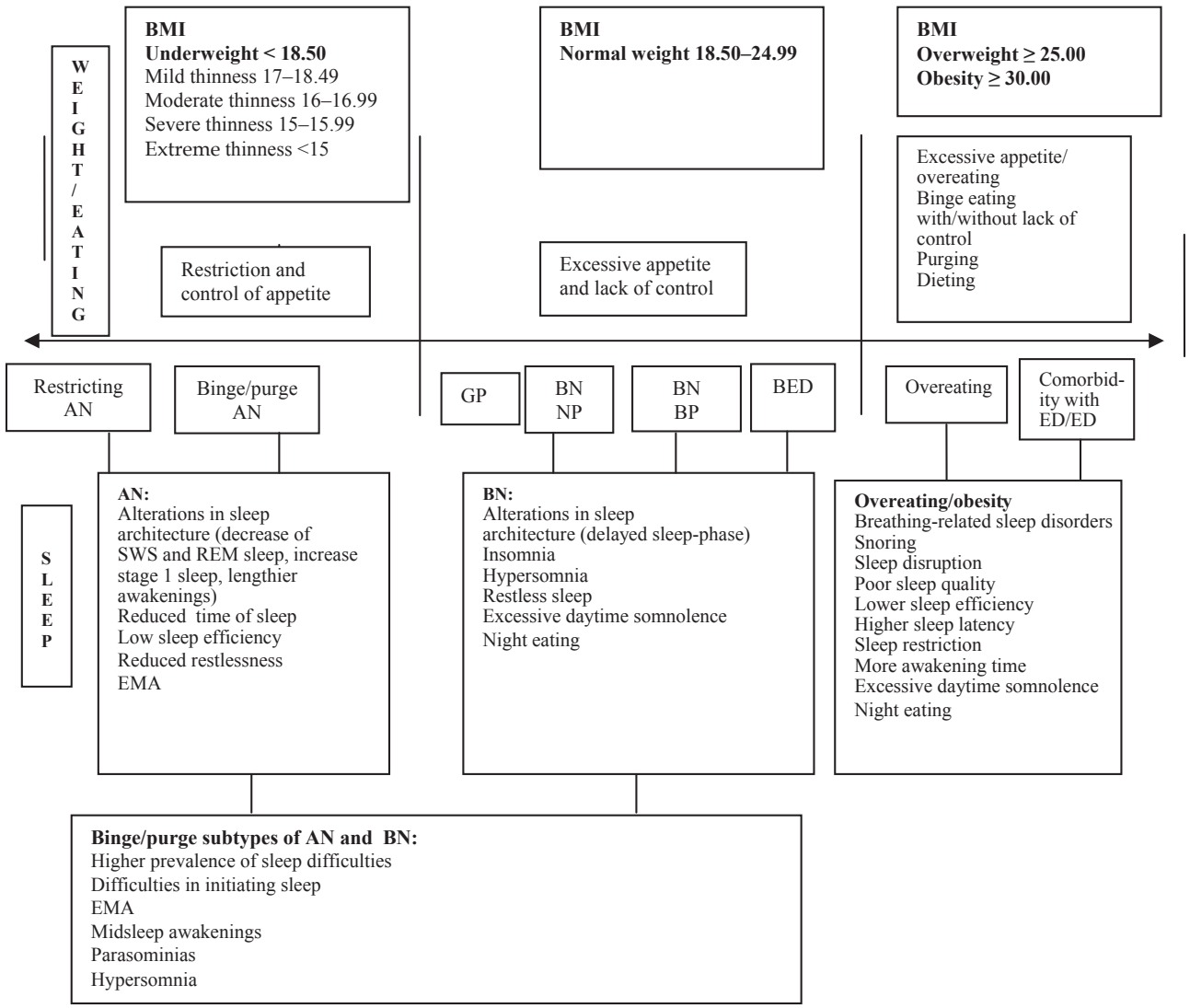
Although clinical judgment is necessary to evaluate a body weight below normal or below the minimal expected level (DSM-V, criterion A), BMI is used to operationalize the levels of thinness severity for adults (BMI (kg/m^2) for low weight <18.5; BMI for thinness ≤17.0) (APA, 2013) (Figure 1) or the corresponding BMI-for-age percentiles for children and adolescents (APA, 2013 criterion A).

The essential features of BN are recurrent episodes of binge eating accompanied by a lack of control over feeding, and use of inappropriate weight gain compensatory behaviors.

There are two subtypes of AN (APA, 2002): the restricting subtype (AN-R) is characterized by excessive caloric restriction whereas the binge-eating/purging subtype (AN-BP) is characterized by binge eating and purging. Also, two subtypes of BN are described, purging (BN-P) and non-purging (BN-NP), during current episodes of BN.

Binge eating disorder is characterized by recurrent episodes of consumption of unusually large amounts of food in a discrete period of time, while feeling that eating is out of control in the absence of extreme weight control behaviors, as seen in BN. Binge eating is a symptom of BED and can be also a symptom of BN, AN-BP subtype, and NES.

Although AN and its subtypes, BN and its subtypes, and BED involve different eating behavior disturbances, a common



BMI = body mass index (kg/m^2); AN = anorexia nervosa; BN = Bulimia nervosa; BN NP = Bulimia nervosa - non purging; BN BP = Bulimia nervosa – binge purging; BED=Binge eating disorder; BMI = Body mass index; GP = Eating behavior disturbances in the general population subjects; EMA = Early morning awakening; SWS = Slow wave sleep; REM = Rapid eye movement sleep.

FIGURE 1 The continuum of eating disorders and weight and associated sleep difficulties.

characteristic of AN patients is the maintenance of severe caloric deficits necessary to continue low weight, whereas BN and BED patients usually maintain weight in a normal range or may even gain weight (Figure 1).

Clinical observations of AN patients' sleeping habits considered that usual symptoms are interrupted sleep and early morning waking (Crisp, Stonehill, & Fenton, 1971; Dally, 1969). Less frequently, initial insomnia might occur in anorectic patients. Anorectic binge-eating/purging subtype patients (AN-B/P) may also have initial insomnia and nocturnal sleep waking to overeat (Dally, 1969).

Objective sleep studies of sleep characteristics in AN patients with low body weight showed alterations in sleep architecture, such as decreased amounts of slow wave sleep (SWS) (Lacey, Crisp, Kalucy, Hartman, & Chen, 1975), reduction of rapid eye movement (REM) sleep (Delvenne, Kerkhofs, Appelboomfondu, Lucas, & Mendlewicz, 1992; Lacey et al., 1975), insomnia, especially early morning waking, reduced sleeping time, especially in the last 4 h of the night, reduced restlessness (Lacey et al., 1976), low sleep efficiency, and lengthier awakening (Delvenne et al., 1992).

More often than controls, BN patients report insomnia, specifically difficulty falling asleep and early morning awakening, restless sleep and excessive daytime sleepiness (Latzer, Tzischinsky, Epstein, & Klein, 1999). Bulimics (BN and BED) also have sleep disruptions for binge eating

at night after having fallen asleep, with total or partial amnesia the next morning or total awareness of the episode. Studies with objective sleep measures (actigraphic records) showed they tend to fall asleep and wake up in the morning about 1 h later than healthy controls, which was related to binge-purge, particularly in the evening or at night (Latzer et al., 1999). However, some studies using objective sleep measures of sleep did not replicate these findings and showed no significant differences in sleep characteristics between AN and BN subjects and healthy controls (Lauer, Krieg, Riemann, Zulley, & Berger, 1990). With respect to electroencephalogram (EEG) sleep laboratory studies, Hudson et al. (1987) found only a trend toward increased REM density in the first REM period among bulimic subjects compared with controls, which was not confirmed by others. Levy, Dixon, and Schmidt (1987) found no significant differences between BN and AN patients and healthy control subjects with respect to REM sleep, and Walsh, Gotez, Roose, Fingeroth, and Glassman (1985) found no significant sleep differences between normal weight bulimic patients and controls.

Subjective and objective sleep problems are also associated with BED (Tzischinsky, Latzer, Epstein, & Tov, 2000). Binge eating disorder in obese patients was associated with self-reported snoring, midsleep awakenings, excessive daytime somnolence, sleepiness, and restless sleep (Tzischinsky et al., 2000). Objective sleep assessment by actigraphs revealed that BED patients had significantly lower sleep quality than normal-weight non-binge eater control subjects, as indicated by sleep efficiency, true sleep time, longest episode of continuous sleep, minutes awake during sleep, and minutes of zero activity counts (Tzischinsky et al., 2000).

Only a few studies take into account BN and AN subtypes. The study by Delvene, Kerkhofs, Appelboomfondu, Lucas, and Mendlewicz (1992) is an exception. A comparison in EEG variables of AN patients and controls revealed that AN patients had reduced REM sleep and a comparison of AN restricting and bulimic subtypes revealed that bulimics anorectics had an increase in stage 3 sleep. A recent transversal study of Kim and colleagues (Kim et al., 2010) using self-reported sleep measurements explored the difficulties of falling asleep, midsleep awakening, early morning awakening, parasomnia, and hypersomnia across different ED categories and subtypes in a sample of female ED patients. Sleep disturbances were reported by 50.3% of ED patients, the most common of which were difficulties in initiating (32.5%) and maintaining sleep (17.75%). Although there was no significant difference between AN and BN patients in global sleep disturbance prevalence (58.3% versus 57.3%), those with binge-eating/purging subtypes had significantly more sleep disturbances (56.8% versus 34.1%) irrespective of having an AN/BN diagnosis. Kim et al. (2010) showed that binge and purgative behaviors are particularly relevant to eating disturbances and sleep difficulties irrespective of AN or BN diagnosis. Both AN-B/P and BN-P were associated with more severe eating disturbances and a higher prevalence of difficulties in initiating sleep, early morning awakening, parasomnias, and hypersomnia than AN-R, BN-NP, and ED not otherwise specified (ED-NOS). Moreover, a higher prevalence of midsleep awakenings were observed in AN-B/P subjects compared with AN-R, BN-NP, and EDNOS, and in BN-P subjects compared with AN-R and BN-NP. These findings suggest a strong association between sleep disturbance and disordered eating, particularly in bulimic/purgative behaviors. Sleep disturbances in ED are also associated with high clinical severity of ED symptoms (Kim et al., 2010), including a high prevalence of binge eating and vomiting, and high levels of global eating disturbances (Eating Disorders Inventory–2 total scores) (Kim et al., 2010). Alterations in the sleep patterns of AN patients may be due to endocrine and metabolic disturbances related to the pursuit of thinness; to nutritional deficits, starvation, and consequent weight loss; and particularly to the occurrence of overeating and purging, as suggested by Kim et al. (2010). On the other hand, the overeating and purgative behaviors in subjects with BB may cause rapid metabolic and neuroendocrine changes that lead to abnormal sleep patterns. Future research on sleep in ED patients might consider ED subtypes.

Night Eating Syndrome and Sleep

The association between eating behavior disturbance and sleep difficulties is also supported by NES, which is characterized by recurrent episodes of night eating, as manifested by eating after awakening from sleep or excessive food consumption after the evening meal (APA, 2013) (Table 1). Moreover, objective measures of sleep showed that this pattern of disordered eating occurs during non-REM sleep and is associated with low sleep efficiency (Wal, 2012).

It was first described in obese female patients by Stunkard, Grace, and Wolff (1955). Since then, its criteria have been revised and modified several times because they were not consensual. Therefore, a group of experts who recently met during the First International Night Eating Symposium proposed a set of diagnostic criteria for NES (Allison et al., 2010) to be tested in research and clinical practice (Wal, 2012) (Table 1). In 2013, the NES diagnostic category was included in the fifth edition of the *Diagnostic Manual of Mental Disorders* (DSM-5) (APA, 2013) within the category Other Specified Feeding or Eating Disorder, which is proposed to be used in situations in which the symptom presentation does not meet the criteria for any specific feeding and eating disorder (Table 1).

Night eating syndrome is often a long-lasting problem (Wal, 2012) that can occur in normal weight, overweight/obese subjects, in subjects with current or lifetime eating disorder diagnoses, and in those with sleep disorder diagnoses.

TABLE 1 Night Eating Syndrome Characteristics

Group of Experts (Allison et al., 2010)[a]	DSM-5 (APA, 2013)
(A.) Daily pattern of eating, characterized by significantly increased intake in the evening and/or nighttime, as manifested by:	Recurrent episodes of night eating, as manifested by eating after awakening from sleep or by excessive food consumption after the evening meal
(A.1.) Evening hyperphagia (consuming at least 25% of food intake after the evening meal and/or at least two episodes of awakenings with nocturnal eating per week) and/or	
(A.2.) Episodes of awakenings with nocturnal eating	
(B.) Presence of awareness and recall of evening and nocturnal eating episodes must be observed	There is awareness and recall of eating
(C.) Three of the following five symptoms must be present for an NES diagnosis:	–
(C.1.) Morning anorexia (lack of desire to eat in the morning and/or omission of breakfast on four or more mornings per week)	
(C.2.) Strong urge to eat between dinner and sleep onset and/or during the night	
(C.3.) Sleep symptoms (sleep onset and/or maintenance insomnia on four or more nights per night)	
(C.4.) The person must believe that one must eat to initiate or return to sleep	
(C.5.) Frequently depressed mood and/or worsened mood in the evening	
(D.) Functioning impairment or significant distress associated with the disorder	Night eating causes significant distress and/or impairment in functioning
(E.) Maintenance of the disorder for at least 3 months	–
(F.) The disorder must also not be secondary to substance abuse/dependence, medical disorder, medication, or another psychiatric disorder	The disordered pattern of eating is not better explained by binge eating disorder or another mental disorder, including substance use, and is not attributable to another medical disorder or to an effect of medication
–	The night eating is not better explained by external influences such as changes in the individual's sleep–wake cycle or by local social norms

[a]*Group of Experts Meeting, during the First International Night Eating Symposium.*

In a sample of women undergoing treatment for obesity, Peixoto (2013) showed that 57% of subjects revealed morning anorexia, 1.2% consumed more than 50% of daily food in the evening, 62.9% have the urge to snack after dinner, 6.7% have cravings or urges to eat when they wake up at night, and 7.9% need to eat to get back to sleep when they wake at night (Night Eating Questionnaire (NEQ), Allison et al., 2008). In these patients, night eating (NEQ total score) was positively associated with short sleep duration, sleep deficit, insomnia, and daytime somnolence (Peixoto, 2013).

The prevalence of NES in obese weight loss patients generally ranges from 4.3% to 15% (Colles, Dixon, & O'Brien, 2007; Kuldau & Rand, 1986) but may exceed from 26% (Rand and Kuldau, 1993) to 64% (Stunkard et al., 1955). Allison et al. (2006), using a semi-structured interview, found that 1.9% of obese presurgery candidates met diagnostic criteria for a strict definition of NES and 8.9% across all definitions of NES; but its prevalence may exceed 42% in these patients (Wal, 2012).

In referrals to an eating disorders clinic over 3 years Tzischinsky and Latzer (2004) found that 5% met diagnostic criteria for NES. Moreover, the prevalence of NES among patients with BED was 16%, among patients with BN 9%, and among patients with AN binge-purge type 0% (Tzischinsky & Latzer, 2004). Stunkard et al. (1996) also observed a similar prevalence of NES (15%) in women with BED. In women reporting binge eating at least once a week, the prevalence of NES was 37% (Colles et al., 2007).

The prevalence of NES ranged from 0.4% to 1.5% in adult community samples of all weights (Rand & Kuldau, 1986; Rand, Macgregor, & Stunkard, 1997) and was 1.1% in children aged 5–6 years (Lamerz et al., 2005). In general population subjects, NES was associated with more eating disturbances, sleep difficulties, and psychopathology. Night eating syndrome was associated with a different circadian distribution of food intake, more severe disordered eating, body image concerns, sleep disturbance, greater depressed mood, perceived stress, decreased quality of life, and more frequent Axis I comorbidity, specifically anxiety, mood, and substance use disorders (Lundgren, Allison, O'Reardon, & Stunkard, 2008). In clinical samples of psychiatric outpatients, the prevalence of NES was 12.3% (Lundgran et al., 2006).

Night eating syndrome is also more common among patients with insomnia (Wal, 2012); its prevalence in subjects who were referred to sleep disorder clinics is 5% (Spaggiari et al., 1994) or 6% (Manni, Ratti, & Tartara, 1997).

Obesity and Sleep

Obesity is a general medical condition characterized by an excess of fat mass in the body. This accumulation of adiposity results from an imbalance between energy intake and energy expenditure. In Western societies obesity has reached epidemic proportions and continues to have alarming increases worldwide in both adults and children (e.g., Finucane et al., 2011); it is one of the major concerns for health according to the World Health Organization (WHO).

Body mass index (BMI = weight (kg)/height (meters)^2) is a widely used measure to evaluate global body fat masses. Body mass index is highly and positively correlated with measures of body fat distribution (e.g., circumferences of waist and hips, abdominal sagittal diameter) and therefore is similarly associated with risks of metabolic complications and diseases. Body mass index cutoffs (WHO) are used to define overweight (BMI 25–29.9) and obesity (BMI ≥ 30) (Figure 1). Overweight/obesity could have many causes and contributing factors (e.g., genetic factors, low physical activity, availability of fast food in Western societies) and eating disorder behaviors can be included among these factors. Low control of food intake, eating patterns, and eating preferences of obese subjects might favor an increase in energy intake, leading to weight gain. They usually eat larger amounts of food than they perceive. Many overweight/obese individuals display eating disorder behaviors such as night eating, dieting, fasting, laxative and diuretic misuse, vomiting, binge eating (e.g., Duncan et al., 2007; Peixoto, 2013), and repeated cycles of restricted diet and overeating, leading to weight fluctuations and/or weight gain. In a sample of obese women, Peixoto (2013) found a high prevalence of eating disorder behaviors: 27.8% showed binge eating episodes with loss of control overeating, 1.5% had vomiting, 5.6% used laxatives to lose weight, and 16% had excessive/compulsive physical exercise to control weight gain. Weight and shape concerns were frequent and 78% of subjects tried to restrict food amounts, 40% of these in all days during the month. A high percentage of BN patients were overweight/obese (e.g., Masheb & White, 2012).

Binge eating disorder is also frequent (Allison et al., 2006). Moreover, a lifetime diagnosis change/crossover might occur. Binge eating is a risk factor for obesity (De Zwaan, 2001) and overweight/obesity may precede BED (Reas & Grilo, 2007) and is a risk factor for BN (Fairburn, Welch, Doll, Davies, & O'Connor, 1997). In addition, the comorbidity between obesity and an ED (BN or BED) confers higher clinical severity to obesity with respect to disordered eating symptoms, sleep disturbance, and psychopathology (e.g., Tzinshinsky & Latzer, 2006).

Overweight and obesity also are often associated with sleep disturbances such as breathing-related sleep disorders (e.g., obstructive sleep apnea (OSA)/hypopnea) in children (Redline et al., 1999) and adulthood (ICSD, 1990), frequent snoring, sleep disruption, difficulties initiating or maintaining sleep, early morning awaking, not getting enough sleep/restless sleep, poor sleep quality (e.g., Peixoto, 2013; Trace et al., 2012; Tzinshinsky & Latzer, 2006), sleep restriction (e.g., Cappuccio et al., 2008; Peixoto, 2013), sleep disruption for eating (e.g., Allison et al., 2006; Schenck et al., 1991), excessive daytime somnolence (EDS) (e.g., Bixler et al., 2005; Resta et al., 2001), feeling sleepy during work or free time, not enough rest, and the need to nap (Trace et al., 2012). Some of these sleep difficulties can be considered risk factors for overweight/obesity (e.g., short sleep duration, NES, NSRED) or a consequence of it (e.g., OSA). Trace et al. (2012) also indicated that most sleep problems of obese women remained significantly associated with obesity when controlling for lifetime depression (all, excluding early awakening and not getting enough sleep).

In objective sleep measures, obese subjects revealed more sleep problems than normal weight controls, including lower sleep efficiency, higher sleep latency, and more awakening time during sleep (Tzinshinsky & Latzer, 2006).

Eating Behavior Disturbances and Sleep Modulation in General Population Subjects

Research on disordered eating and sleep disturbance modulation in community samples is scarce and most of it is cross-sectional.

In the 1950s, a starvation study showed that severe and prolonged dietary restriction in healthy male volunteers can lead to severe physical and psychological problems, including food preoccupation, binge eating episodes, sleep disruption, and a decreased need for sleep (Keys et al., 1950). Makino, Hashizume, Yasushi, Tsuboy, and Dennerstein (2006) in a sample of college students showed that global eating

disturbances and distorted body perception were associated with short sleep duration. Ohayon and Hong (2002) in a sample of subjects from the general population showed that eating before going to sleep was associated with sleep disruption and with non-restorative sleep, and Veldi, Aluoja, and Vasar (2005) in a sample of medical students found that awakening owing to nocturnal eating was associated with poor sleep quality. In a community sample of young adult females, Seigel, Broman, and Hetta (2004) found an association between reports of insomnia, eating disturbances, and concern about body image. Frequent attempts to reduce weight, body image dissatisfaction, feelings of being overweight, fear of becoming fat, binge eating episodes, and the impulse to vomit were significantly associated with difficulties maintaining sleep and with the perception of restless sleep.

Only longitudinal studies are informative about the direction of the causal relationship between sleep and eating problems. In a study of women assessed during and after pregnancy, Ulman et al. (2012) showed that DSM-IV BED symptoms before and/or during pregnancy are associated with sleep problems during pregnancy and with dissatisfaction with sleep 18 months after childbirth.

LONGITUDINAL STUDIES IN GENERAL POPULATION SUBJECTS EXPLORING THE BIDIRECTIONAL ASSOCIATION BETWEEN SLEEP AND EATING DISTURBANCES/BMI: OUR CONTRIBUTION

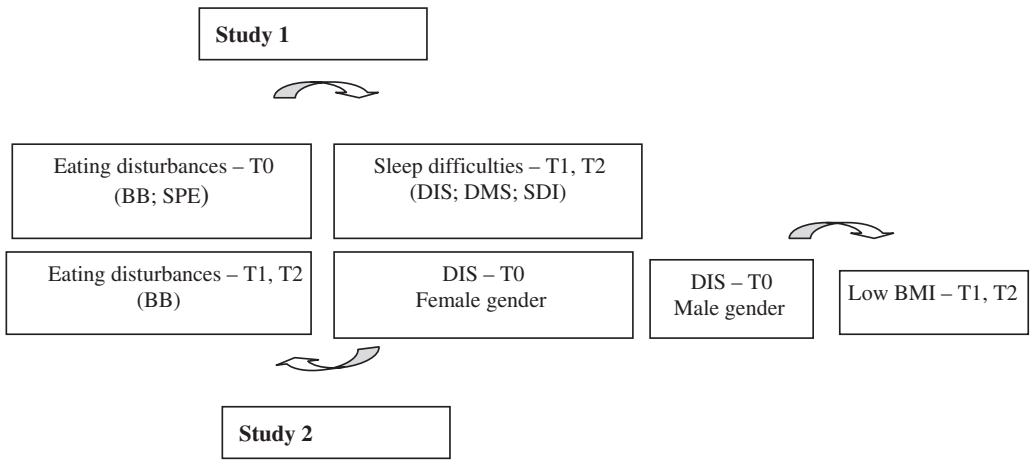
Two prospective studies on the association of eating and sleep disturbance and BMI might clarify their bidirectionality (Bos et al., 2013; Soares et al., 2013). They were performed in the same sample of 870 university students (mean age, 19.59 years; standard deviation, 1.61 years; range, 17–25 years) with both genders represented ($n = 544$). These studies comprised three assessment stages: baseline (T_0; time 0); 1 year (T_1; time 1), and 2 years after the baseline (T_2; time 2). At each stage, subjects completed the same measures (Bos et al., 2013).

Study 1

Bos et al. (2013) explored whether eating disturbances/BMI were predictive of sleep difficulties over time (Figure 2). This study showed that subjects with more severe global disorders of eating at baseline (particularly BB and SPE) revealed more DIS, DMS, and SDI at all stages of the study (baseline, T1, and T2) compared with students with less severe eating-disordered behaviors. Concerning DC, the association with sleep disturbances was less robust. Nevertheless, the group with more severe DC and behaviors at baseline revealed more overall sleep difficulties (SDI) over time than the group with less severe DC. Moreover, the groups with persistent insomnia, remission, and onset of sleep difficulties at T_1 and T_2 revealed more disordered global eating behaviors and more BB and SPE at baseline compared with good sleepers.

Additionally, the group with sleep onset difficulties over time revealed more DC at baseline than did good sleepers.

This study also revealed that BB and SPE are the predictors of long-term difficulties of initiating and maintaining sleep and of persistent insomnia. However, BMI was not a significant predictor of eating disturbances and of sleep difficulties over time (Bos et al., 2013).



The findings from Bos et al. (2013) and Soares et al. (2013) studies; BB = Bulimic behaviours, SPE = Social Preassure to Eat; DIS = Difficulties in initiating sleep; DMS = Difficulties in maintaining sleep; SDI = Sleep Difficulties Index; BMI = Boby Mass Index; T0 = Time 0/baseline; T1 = Time 1/one year after; T2 = Two years after

FIGURE 2 Bidirectional association between sleep and eating disturbances/BMI.

Study 2

Soares et al. (2013) explored whether sleep difficulties are predictive of eating disturbances/BMI (Figure 2). Findings revealed that insomniacs at baseline showed consistently more severe disordered global eating behaviors, DC, BB, and SPE over time (at T_1 and T_2) and also a lower BMI at T_2 than good sleepers. This study also revealed that female gender and DIS at baseline were predictors of BB over time. DC, SPE, and global eating disturbances predictors were less consistent over time. In respect to BMI, consistent predictors overtime were male gender and DIS at baseline.

Results from both of these studies substantiate the bidirectional association between sleep and eating disturbances, particularly difficulties initiating sleep and BB. In contrast, a dual directionality between BMI and sleep disturbance was not observed and only difficulty initiating sleep and male gender were predictive of low BMI.

BODY MASS INDEX VERSUS EATING BEHAVIOR DISTURBANCES ASSOCIATIONS WITH SLEEP

BMI and Eating Disturbances

There is evidence from the literature that BMI is associated with disordered eating in clinical samples and in general population subjects, and BMI is often considered a proxy for eating problems and nutritional deviance. In fact, BMI cutoffs are part of the operational diagnostic criteria of AN (DSM-5, 2013) and are used to define obesity and its severity (WHO). Weight is also part of BN and BED, and maintenance of normal range weight, weight fluctuations, and a tendency to gain weight or to be obese characterize them (Figure 1). With respect to the association between body weight/BMI and sleep patterns findings from literature are mixed; some studies confirm this association and others do not.

Weight/BMI and Sleep

As described in this chapter, several clinical and research findings support an association between underweight (e.g., AN), overweight/obesity, and weight fluctuation (e.g., weight loss, weight gain as observed in BN and in the general population) and sleep problems.

The relation between weight and sleep is supported by experimental studies on the impact of weight gain/loss on sleep with animal models (Guan, Vgontzas, et al. 2008; Jacobs & McGinty, 1971), with healthy males from the general population (Keyes, 1950), and with clinical samples of psychiatric patients, AN patients, and obese patients (e.g., Bixler et al., 2005; Crisp et al., 1971; Dixon, Schachter, & O'Brien, 2001; Resta et al., 2003).

In psychiatric outpatients, weight loss is associated with reduced duration of sleep, more broken sleep, and early waking; inversely, weight gain is associated with longer duration of sleep, unbroken sleep, and later waking (Crisp & Stonehill, 1973). A consistent finding from research is that weight loss in AN patients is accompanied by an increase in sleep difficulties such as insomnia, particularly with middle and terminal insomnia (Crisp & Stonehill, 1973), and with a decreased amount of total sleep (Crisp et al., 1971). Conversely, weight gain weight/restoration in anorectics is accompanied by subjective improvements in sleep (increase in sleep duration and decrease of wake time), confirmed by studies with objective sleep measures (Lauer & Krieg, 2004). More specifically, the last one revealed that weight gain is associated with improvements in sleep continuity and sleep architecture (Lauer & Krieg, 2004): namely, with a decrease in intermittent awake time, an increase in the amount of REM sleep (Lacey et al., 1975; Lauer & Krieg, 1992; 2004), and a reduction in NREM stage 3 sleep for the benefit of stage 4 sleep (Lauer & Krieg, 1992). Improvement in NREM was found to be less consistent with some authors confirming its occurrence. Some authors found them (Lauer & Krieg, 2004) while others did not (Lauer & Krieg, 1992), and they were shown to be unstable throughout weight recovery (Lacey et al., 1975). However, Delvene et al. (1992) in a study with AN, BN, and control subjects, found that sleep EEG variables were not significantly correlated with BMI. A general finding emerged of a relationship between weight loss and weight gain, longer duration of sleep, unbroken sleep, and later waking with weight recovery in ED patients.

In community samples, evidence of BMI/weight and sleep link is mixed. Some studies showed significant positive associations between having a high BMI (e.g., being overweight/obese) and, for example, nocturnal awakening, insomnia, excessive daytime somnolence, less need for sleep in males, and short and long sleep duration (e.g., Bjorvatn et al., 2007; Cappuccio et al., 2008; Gangwisch et al., 2005; Lopes, 2011; Ohayon & Hong, 2002; Oyahon & Vecchierini, 2005; Rosmaninho, 2011).

Even an inverse association between BMI and sleep difficulty and sleep duration was reported (Soares et al., 2011; Soares et al., 2013; Xiang et al., 2009) in two studies performed on university students (Soares et al., 2011; Soares et al., 2013) and on females (but not in males) from the general population of China (Xiang et al., 2009).

However, there are also several studies with clinical samples of ED, obese patients, NED patients (e.g., Delvenne et al., 1992; De Zwaan, Burgard, Schenck, & Mitchell, 2003; Lauer & Krieg, 2004; Peixoto, 2013), and persons from the community whose findings did not indicate an association between BMI and sleep problems (e.g., Lamerz et al., 2005; Rand et al., 1997; Seigel et al., 2004).

Eating Disturbances, Weight/BMI and Sleep Difficulties

An additional finding from the literature is that disordered eating and weight/BMI could be differently related to sleep disturbances, as suggested by findings from studies exploring both disordered eating behaviors and BMI and sleep difficulties in the same sample.

In a sample of obese women undergoing treatment for obesity, Peixoto (2013) found no significant associations between BMI and sleep duration, sleep needs, sleep deficit, insomnia, and daytime somnolence (DS) although these sleep difficulties were associated with eating disturbance. Using other anthropomorphic measures of body adiposity considered to be more accurate for evaluating central obesity, such as abdominal sagittal diameter and neck circumference, the author found that they were positively associated with self-reported sleep deficit and sleep needs, respectively. However the correlations were poor.

In the transversal study of Soares et al. (2011), low BMI did not contribute significantly to an explanation of sleep difficulty and to the likelihood of reported insomnia symptoms in both genders. Regardless of this, sleep difficulties were associated with and were significant predictors of eating disturbances in both genders, and subjects with insomnia symptoms of both genders also revealed more disordered eating behaviors and consistently more BB.

Lopes (2011) in female university students found that BMI was not significantly associated with sleep restriction. However, sleep deficit, BMI, and self-reported poor psychological/mental health were shown to have a significant contribution to BB explanation. Sleep deficit and sleep duration also were predictive of DC and global eating disturbances, but were mediated by poor psychological/mental health.

Considering the two studies that explored the bidirectional association between sleep and eating disorders (Bos et al., 2013; Soares et al., 2013), findings indicated a consistent bidirectional association between disordered eating behaviors, particularly BB, and sleep disturbances over time, particularly DIS. In contrast, a dual directionality between BMI and sleep disturbances was not observed. Therefore, low BMI is not a significant predictor of sleep difficulties over time (Bos et al., 2013), even though sleep difficulties at baseline and male gender were predictive of lower BMI over time (Soares et al., 2013).

The different association between BMI and sleep difficulties and between eating behaviors and sleep indicate that BMI may not be a good proxy for eating disturbances or their association with sleep disturbances. Therefore, it is possible that BMI may cluster with disordered eating behaviors and nutritional deviance, particularly at the extremes of disordered eating and weight continuum, corresponding these extremes to AN and obesity. However, this is not the case in ED such as BN, BED and EDNOS, which are characterized by the maintenance of a normal range weight or by weight fluctuations or even a tendency to gain weight in consequence of cycles of restricted diet and overeating, despite the occurrence of severe disordered eating.

POTENTIAL MECHANISMS OF ASSOCIATION

Psychological Correlates of Eating Behavior Disturbances and Sleep Problems

Sleep and eating disturbances are complex phenotypes with a multifactorial, biopsychosocial determination that are not yet completely known. In a previous study (Soares et al., 2013) using a transdiagnostic perspective that is considered a first step toward assessing common and specific processes of psychopathology, we suggested that psychological arousal might have a role in the bidirectional association between eating disturbance and sleep difficulties (Soares et al., 2011) (Figure 2). Some personality traits (e.g., perfectionism; neuroticism, impulsivity, novelty seeking), maladaptive cognitive processes and attributional styles, maladaptive mechanisms of coping with stress, emotion regulation mechanisms, and affective dysregulation (e.g., tendency to experience anxiety, hostility, and depressive affect) might contribute to an increase in the impact of life events and stress, and to the determination/intensification of psychophysiological arousal (Soares et al., 2013). This might be related to psychological distress, including negative affect, sleep, and eating disturbances. In fact, previous studies showed that stress and sleep disruption are completely mediated by psychophysiological arousal (Morin, Rodrigue, & Ivers, 2003) and that stress and psychological negative states (e.g., negative affect; anxiety and depression) interfere with efforts to maintain a restricted diet (Stice, 2001) and are related to overeating, a preference for sweet and fat food (Adam & Epel, 2007), emotional eating, loss control over eating, and binge eating episodes (Stice & Shaw, 2002). Intensification or maintenance of psychophysiological arousal can be observed by a feedback process, by worries or concerns about sleep disruption and daytime consequences, and by feelings of failure and concerns about one's loss of control over eating and weight and shape (Soares et al., 2013) (Figures 3 and 4).

With the goal of exploring contributing factors to pre-sleep arousal (Portuguese version of the Pre-sleep Arousal Scale (PSAS)) (Azevedo et al., 2010) and the mediating role of pre-sleep arousal on the association of eating and sleep disturbance, we performed a study on a sample of 468 unmarried female medical and dentistry students, aged 17–24 years (data not published).

Results showed that introversion (Eysenk Personality Inventory–12), negative affect (Profile of Mood States), worries interfering with sleep (loss of sleep over

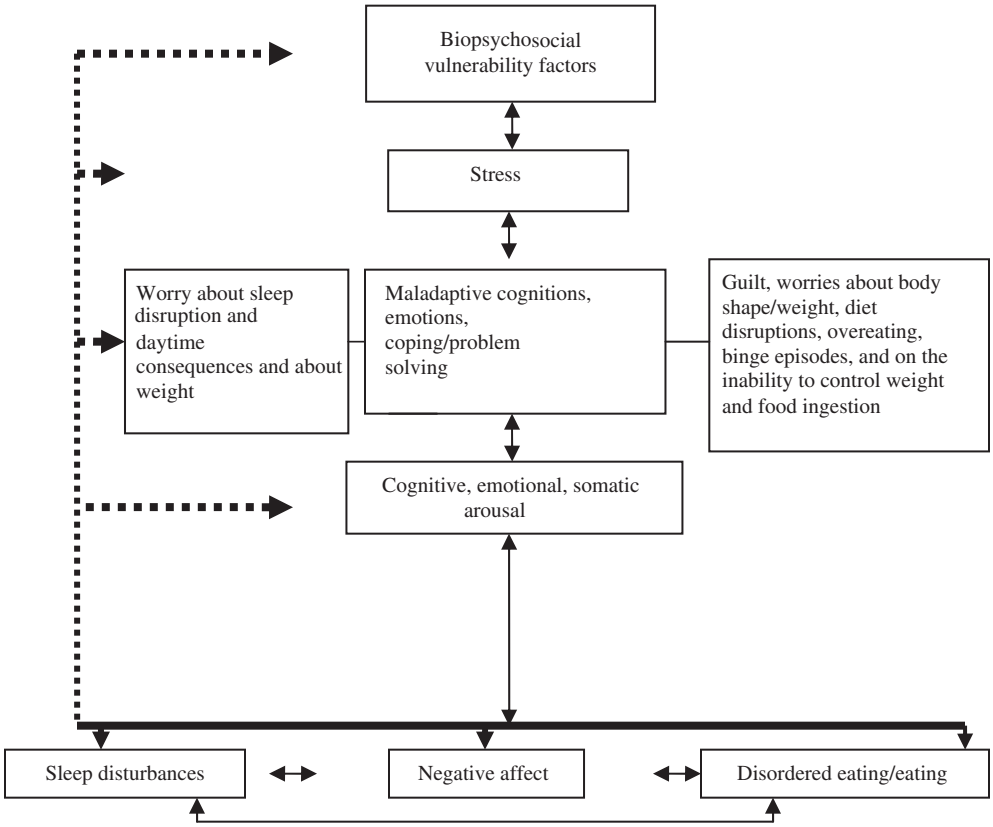


FIGURE 3 Model of possible biopsychosocial factors related to both disordered eating and sleep difficulties.

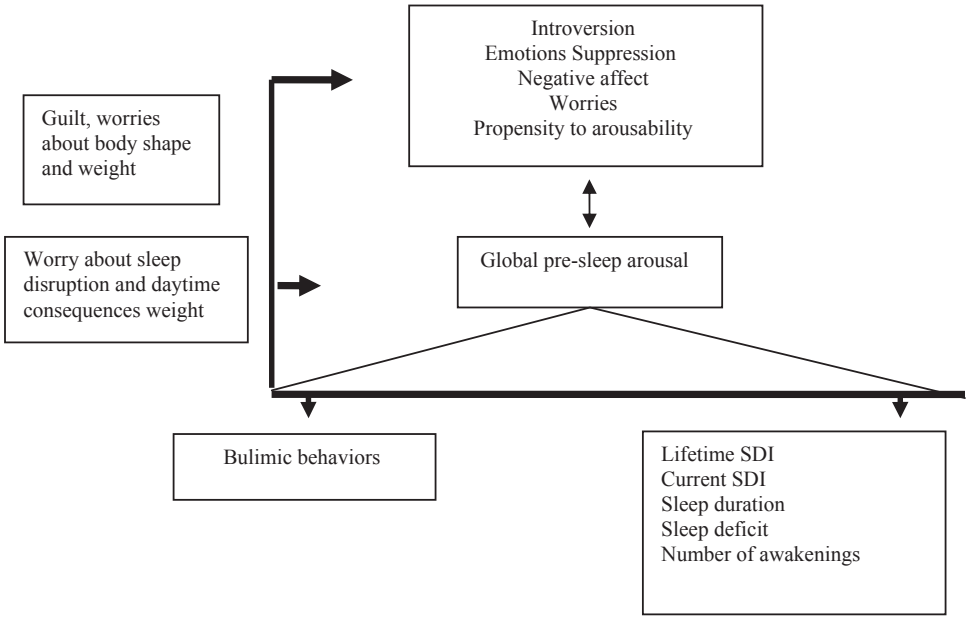


FIGURE 4 Mediation role of pre-sleep arousal in the association of eating and sleep disturbance (including our findings).

worries), arousal propensity (Arousal Pre-Sleep Scale), and emotion suppression (Emotions Regulation Questionnaire) were the PSAS total score significant predictors in a model that explained 41.2% of its variance. Unexpected results were that perfectionism and impulse strength were not significant predictors of pre-sleep arousal.

As we hypothesized, the global pre-sleep arousal (PSAS total score) was independently associated with both

eating disturbances (Eating Attitudes Test–25) (Pereira et al., 2008) and sleep difficulties. Global pre-sleep arousal was significantly associated with global eating disturbances and BB dimension and with sleep duration, sleep deficit, sleep depth and quality, sleep latency, number of awakenings from sleep, difficulties initiating and maintaining sleep, and excessive daytime somnolence. Because DC, SPE, and BMI were not associated with global pre-sleep arousal, mediation analysis was not performed with respect to these dimensions. Because BB was associated with pre-sleep arousal and both of these were associated with global sleep difficulties (SDI), lifetime and current difficulties initiating and maintaining sleep, sleep duration, sleep quality, sleep flexibility, number of night awakenings, and sleep deficit mediation analyses were performed between BB and these sleep problems using PSAS total score as a mediator.

Results from mediation analysis confirmed the partial mediation role of global pre-sleep arousal (PSA–total score) in the association between BB and sleep duration and its total mediation in the association between BB and both lifetime and current global sleep difficulties (SDI), number of sleep awakenings, and sleep deficit. The mediating role of pre-sleep arousal was not significant in the association of BB with sleep quality and sleep flexibility (Figure 4).

Psychological and mental health (e.g., depression and anxiety disorders) also might have a role in the interrelation of eating and sleep disturbance (Soares et al., 2013) but it was not explored.

Feeding Behavior, Sleep, and Arousal: Neurobiologic Mechanisms

Evidence from multiple sources indicates that sleep and metabolism are largely regulated by the same brain circuits, and that these circuits are also part of stress response and reward systems, with the hypothalamus playing a central role in the modulation of these multiple interacting homeostatic processes and mechanisms (Adamantidis & de Lecea, 2008; Boutrel & de Lecea, 2008).

The lateral hypothalamus area (LH) has a key role in the regulation of ingestive behavior and sleep–waking regulation. Some peptides are expressed in the brain only by neurons in this area: melanin concentrating hormone (MCH) and hypocretins 1 and 2 (Hcrt 1/Hcrt 2) (also known as orexins A and B) (Sakurai et al., 1998). Activation of Hcrt neurons has postsynaptic excitatory properties, whereas MCH neurons are thought to have the opposite effect (Sakurai, 2007).

Hypocretin neurons have widespread projections throughout the brain, especially to areas involved in energy homeostasis, arousal, and brain reward (Boutrel & de Lecea, 2008), including the cortex, hippocampus, amygdala, nucleus accumbens, histaminergic tuberomammillary nucleus (TMN), thalamus, ventral tegmental area (VTA), locus coeruleus (LC), and raphe. In turn, afferents to these neurons project from multiple areas linked to the regulation of the sleep–wake cycle, energy homeostasis, and motivation such as the basal forebrain, bed nucleus of the stria terminalis, lateral septum, preoptic area, and posterior hypothalamus (Yoshida, McCormack, Espana, Crocker, & Scammell, 2006).

Melanin concentrating hormone neurons have numerous roles, and their involvement in feeding behavior and energy homeostasis is well documented (Pissios, Bradley, & Maratos-Flier, 2006). Melanin concentrating hormone has acute short-term orexigenic properties and the MCH system is upregulated after fasting. Available evidence demonstrates that activation of the MCH system decreases energy expenditure.

Appetite is regulated by the interaction between metabolic and hormonal signals in the central nervous system, mainly in the LH. This brain region regulates energy homeostasis (i.e., food intake and metabolism) by sensing circulating hormones (e.g., leptin and ghrelin) and by integrating autonomic, endocrine, and environmental signals into coherent goal-directed behaviors such as feeding (Adamantidis & de Lecea, 2009). Leptin is a satiety hormone produced by adipose tissues that inhibits hypothalamic arcuate neurons that coexpress neuropeptide Y (NPY) and agouti-related peptide (AgRP) and activate proopiomelanocortin (POMC) neurons that also coexpress cocaine- and amphetamine-related transcripts (CART). In contrast, ghrelin, a hormone from the digestive tract, has the opposite effect and is appetite-stimulating. Thus, activation of POMC/CART and NPY/AGRP neurons induces anorexigenic and orexigenic properties, respectively.

With respect to the association between sleep and ingestive behavior, we know that sleep duration and the length of a sleep–wake cycle are inversely correlated with brain metabolic rate across species (Savage & West, 2007). Also, sleep disturbances (e.g., sleep reduction) are associated with hormonal imbalances that may result in metabolic disorders, including obesity and diabetes (Knutson & Van Cauter, 2008). In this context, epidemiological studies have shown a strong association of short sleep duration with lower leptin and higher glucose and ghrelin levels (Chaput, Després, Bouchard, & Trembley, 2007; Taheri, Lin, & Mignot, 2004). Such peripheral signals activate NPY/AgRP neurons and inhibit POMC/CART neurons (Abizaid & Horvath, 2008). This result in a feeding signal, which may be responsible for the higher BMI and increased incidence of type 2 diabetes reported after protracted sleep disturbance (Penev, 2007).

Thus, according to Adamantidis and de Lecea (2008), the Hcrt and MCH systems have an antagonistic function in sleep and metabolism. Activation of the Hcrt system promotes wakefulness and induces energy expenditure. In contrast, the MCH system is thought to promote energy conservation and to be a sleep-promoting system, possibly by inhibiting arousal centers of the brainstem and posterior

hypothalamus or by activating sleep-promoting neurons of the anterior hypothalamus (Adamantidis et al., 2008; Modrrousta, Mainville, & Jones, 2005; Verret et al., 2003).

The scope of functions in which the Hcrt system is implicated largely exceeds the regulation of sleep and eating. Multiple evidence has shown that the Hcrts are critical for the maintenance of arousal. By arousal, we mean a state of heightened cortical responsiveness to sensory input mediated by activation of the ascending reticular formation located in the brainstem, accompanied by an increase in physiological activity (Adamantidis & de Lecea, 2009).

Behavioral arousal is a key component of the stress response and recent data indicate that the hypocretinergic system may also be a component of response of the hypothalamo–pituitary–adrenal (HPA) axis. Activation of the HPA axis consists of increased release of corticotropin-releasing factor (CRF) from the paraventricular nucleus of the hypothalamus (PVN), stimulating adrenocorticotropin hormone (ACTH) secretion from the pituitary, which afterward increases secretion of adrenal corticosteroids.

Intracellular recordings of Hcrt neurons indicate that CRF, which is responsible for initiating the central stress response, directly depolarizes hypocretinergic cells (Winsky-Sommerer et al., 2004). This effect is likely mediated through CRF-R1.

The fact that Hcrt deficiency results in narcolepsy in humans, dogs, and rodents suggests that the Hcrt system is particularly important in the maintenance of wakefulness (Tsujino & Sakurai, 2009). The brain of narcoleptic patients is practically devoid of Hcrt-producing neurons (Thannickal et al., 2000) and Hcrt peptide infusion promotes wakefulness (Sakurai, 2007).

Close partners in the regulation of wakefulness are noradrenergic, serotonergic, and histaminergic neurons (Anaclet et al., 2009; Passani, Giannoni, Bucherelli, Baldi, & Blandina, 2007). The last is particularly important and regulates basic homeostatic and higher functions including cognition and circadian and feeding rhythms. Furthermore, one of the major outputs of the Hcrt system that promotes wakefulness is direct activation of histaminergic neurons that are localized exclusively in the TMN, in the posterior hypothalamus. This area of hypothalamus has only recently been recognized as an important waking center (Lin, Sergeeva, & Haas, 2011).

Thus, in addition to their crucial role in stabilizing the sleep–wake cycle, enhanced Hcrt neuronal activity could promote feeding behavior, arousal, and increased energy expenditure acting in part via activation of several mechanisms, including the activation of arousal centers in the brain and increasing sympathetic tone. It is possible that these mechanisms could also be activated via cognitive arousal.

The Hcrt system is also a major component of natural reward associated with feeding behavior, and its activation can increase hedonic feeding (Adamantidis & de Lecea, 2008). It is possible that sleep and metabolism are also regulated through reward pathways of the brain. Hypocretins and MCH might interact with brain reward pathways to modulate arousal and food-seeking behaviors (Boutrel & de Lecea, 2008; Georgescu et al., 2005). This suggests a pathophysiological role for these circuits in patients with night eating syndrome (NES), NSRED, and narcolepsy, who have sleep perturbation associated with night feeding (Chabas et al., 2007).

The Hcrt and MCH systems, acting in concert with other neurotransmitter systems (serotonergic, histaminergic, dopaminergic, and noradrenergic), are at the heart of different homeostatic functions, illustrating the intricate relationship between wakefulness, stress reactivity, feeding, and reward systems. Therefore, those systems may constitute potentially new targets for therapeutic interventions in sleep disorders, eating disorders, addiction, and emotional problems (Tsujino & Sakurai, 2009).

DISCUSSION

Sleep disturbances, disordered eating behaviors, and BMI are interrelated. There are numerous findings in the published literature supporting the association between eating and sleep disturbances in animal models, as well as in clinical populations of eating disorders and obesity patients, in patients with NES/disorders, and in patients with sleep problems, as well in community samples. Therefore, it is time to explore their bidirectional association and mediation factors.

Results from two recent studies in healthy student populations substantiate the bidirectional association between sleep and eating disturbances (Bos et al., 2013; Soares et al., 2013). Difficulties in initiating sleep (and female gender) at baseline were significant predictors for global eating disturbances and BB 1 and 2 years later (Soares et al., 2013); conversely, BB and social pressure to eat are predictors for overall sleep disturbance, difficulties initiating and maintaining sleep, and persistent insomnia over time (Bos et al., 2013). The interrelation between DC and sleep difficulties was less consistent over time (Bos et al., 2013; Soares et al., 2013).

Both of these studies suggested that the interrelation between disordered eating and sleep difficulties consistently involves BB and difficulties in initiating sleep. The association between sleep difficulties and BB was confirmed by studies in clinical samples of AN and BN patients (e.g., Kim et al., 2010), in undergraduate students (Lopes et al., 2011; Soares et al., 2011), and in young females from the general population (Seigel et al., 2004). In a study on subjects with an eating disorder, Kim et al. (2010) observed an association between sleep difficulties and eating disturbances, particularly bulimic/purgative symptoms, irrespective of the AN or BN diagnosis

(Kim et al., 2010). In a study on young adult females, Seigel et al. (2004) showed that body image dissatisfaction, feelings of being overweight, fear of becoming fat, repeated attempts to reduce weight, and bulimic/purgative behaviors such as binge eating and the impulse to vomit after eating were significantly associated with difficulties in maintaining sleep and with non-restorative sleep. Studies with university students also confirm the role of sleep difficulties in eating disturbance modulation, difficulties in initiating sleep (Soares et al., 2011), and sleep debt (Lopes et al., 2011) particularly related to eating-disordered behaviors and especially to BB. A lifetime history of BE was also found in persons with current sleep problems (Trace et al., 2012), and previous and current BED symptoms were associated with current sleep problems and prospectively with dissatisfaction with sleep (Ulman et al., 2012).

Globally, these findings on eating and sleep association suggest that sleep and eating problems may cluster together (Tzischinsky & Latzer, 2004; Winkelman et al., 1999) throughout a continuum of severity.

In contrast, bidirectionality between BMI and sleep disturbances was not observed. Sleep difficulties at baseline are associated with current and long-time lower BMI (Soares et al., 2011; Soares et al., 2013), but the inverse association is not confirmed. Lower BMI is not a significant predictor of sleep difficulties over time (Bos et al., 2013).

Reports on the association of sleep and BMI in clinical samples and in community samples are mixed and do not show consistent associations between sleep patterns and body weight/BMI. However, the inverse association between sleep difficulties and BMI (Bos et al., 2013; Soares et al., 2013) is unexpected considering the findings of most studies on sleep restriction and weight/obesity, which revealed that short/long sleep and weight increase/obesity are associated (e.g., Cappuccio et al., 2008; Gangwisch et al., 2005). These findings suggest that non-clinical samples of young adults from the general population behave in the same way as clinical samples of AN patients (Dally, 1969). These results may also indicate that difficulties initiating or maintaining sleep and short sleep duration may not correlate (Kripke, Garfinkel, Wingard, Melville, & Marler, 2002), and consequently, their association with weight/obesity may be different. Nevertheless, our findings were similar to those of Xiang et al. (2009), which revealed that Chinese female short sleepers (not males) had lower BMI than medium and long sleepers, after controlling for age and psychiatric disorders.

An additional finding from these two studies exploring the bidirectionality (Bos et al., 2013; Soares et al., 2013) is that BMI and eating disturbances did not overlap with respect to sleep disturbance prediction. Studies simultaneously exploring an independent association of BMI and eating disturbances with sleep disturbances in the same sample might clarify whether BMI is always a proxy for eating disturbances in this association. Results from these studies are in line with our findings. They also indicated a high positive association between BMI and disordered eating, although both of these are differently related to sleep disturbances.

Therefore, there is a continuum of weight, from underweight/severe thinness to overweight/extreme obesity (Figure 1). This continuum of weight is accompanied by several eating disturbances and disorders: AN-R, AN-BP, BN-NP, BN-P, BED, ED-NOS, obesity, obesity with comorbid eating disorders, and disordered eating behaviors in subjects from the general population (Figure 1). The overlap between eating disturbances and BMI might be higher in the extremes of the weight continuum: namely, AN and obesity. This overlap might be lower in BN, BED, and EDNOS patients, as well as in general population subjects with eating behavior disturbances, because in these subjects, disordered eating behaviors may be observed despite maintaining weight within normal ranges. This continuum of weight and eating disturbances might be accompanied by sleep difficulties (Figure 1). Therefore, BMI could not be a proxy of eating disturbances in their association with sleep disturbances, particularly in cases in which low overlap between both of these is observed. Thus, it may be possible that in our sample of healthy young adults from the general population, BMI and eating disturbances are differently related to sleep difficulties as a consequence of the low overlap between BMI and eating disturbances.

It is also possible that BMI and eating disturbances have different correlates/risk factors, as well as different mediators that might function as covariates/mediators/confounding factors in their link with sleep disturbances, such as, for example, age, gender, and physical and psychological/mental health. In fact, we found a different influence of gender on the association between sleep difficulties and, respectively, BMI (male gender) and eating disturbances (female gender) (Soares et al., 2013). A gender effect is also observed by Lopes et al. (2011) in a sample of university students, where high body mass index was associated with low sleep needs only in males, and by Xiang et al. (2009) in a representative sample from the Chinese general population, in which short sleep duration and BMI were only observed in females. The age might be a correlate or risk factor that can influence predictors and outcomes by its effect on BMI (increased with age), eating disturbances (higher risk and prevalence in adolescence and young adults), and sleep characteristics. Lopes (2011) found a robust association between poor physical health and BMI and between poor psychological/mental health and eating disturbances (BB were associated with both poor physical and psychological/mental health).

The observation that BMI is associated with eating disturbances but is not a proxy for eating disturbances on their association with sleep disturbances also might have

implications for research and clinical settings. One implication is that it will be useful to consider more than BMI cutoffs in the classification of obesity. This may require the definition of phenotypes that will simultaneously consider BMI or other measures of adiposity, the occurrence of disordered eating behaviors, and perhaps sleep problems. Sleep problems may also be involved in the maintenance of eating disturbances and in BMI prediction (Bos et al., 2013, Soares et al., 2013). The presence of sleep disturbance was an indicator of eating symptoms and behavior severity in ED patients (Kim et al., 2010). Sleep disturbance may also be an important clinical marker of disordered eating and could be useful in clinical settings, especially for ED in which patients denied eating symptoms (Kim et al., 2010). They may also be a secondary parameter of recovery (Kim et al., 2010).

Neurobiologic mechanisms involved in sleep and metabolism might explain the association or interrelation of sleep and eating behaviors. Sleep and metabolism are largely regulated by the same brain circuits, which are also part of reward systems and stress response, with the complex hypothalamic machinery underlying the interface between the sleep–wake cycle, feeding behavior, reward, arousal, and stress reactivity. Hypothalamic peptidergic neurons such as the orexin system interact with systems that regulate emotion, reward, and energy homeostasis. This might underline the association between negative emotions, eating under emotional conditions (binge eating episodes and emotional eating), and sleep difficulties/wakefulness.

We hypothesized in a previous study (Soares et al., 2013) that among psychological mechanisms, psychophysiological arousal might have a mediating role in the association between sleep difficulties and eating disturbance. Our study on the mediating role of pre-sleep psychological arousal in the association of eating and sleep disturbances revealed that pre-sleep arousal is a partial/or total mediator of BB and some sleep difficulties (lifetime and current overall sleep difficulties (SDI), sleep duration, sleep deficit, and number of awakenings) but not all. Particularly prone to pre-sleep psychological arousal are individuals with high propensity to arousability, high levels of introversion personality trait, negative affect, and suppression of emotions, revealing maladaptive cognitions such as worries interfering with sleep.

Therapeutic interventions addressing pre-sleep arousal and their correlates may lead to improvements in ED behaviors (e.g., BB), sleep difficulties, and interruption of the circular cycle of associations between both. This interruption can have reflexes in the predictive power of sleep in BMI modulation.

Another implication of our findings is that general practitioner clinicians and specialized clinicians should pay attention to the possibility of coexisting sleep and eating disturbances in ED patients, obese subjects, and subjects from the general population. Effective prevention and clinical interventions in sleep and eating/weight areas might focus on both eating and sleep disturbances, and assess and intervene in both eating and sleep. This may involve resources and knowledge from both sleep and eating/obesity areas.

An additional implication is that prevention and clinical interventions focusing on disordered eating behaviors and sleep difficulties can ameliorate both and prevent a BMI increase or decrease. Treatment and prevention of ED might reduce sleep difficulties; conversely, a decrease in sleep difficulties might reduce the risk of ED and prevent weight gain or loss.

Studies on bidirectionality described here were performed on university students and our findings may not be generalized to other populations. Future longitudinal research on bidirectionality with other populations might contribute to knowledge in the areas of sleep and eating/weight. Investigations should control for the effect of some likely correlates, contributing factors, and mediators that may intervene in sleep and eating and their association, such as, for example, age, gender, physical and mental health, negative affect states, levels of stress, medication, health-related habits (e.g., alcohol, tobacco), patterns of eating close to bedtime, the macro-composition of nourishment, and the level of patients' activities.

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Part II

Obesity and Sleep Apnea

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Chapter 7

Neurocognitive Functions in Patients with Obstructive Sleep Apnea Hypopnea Syndrome

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OBSTRUCTIVE SLEEP APNEA HYPOPNEA SYNDROME

Obstructive sleep apnea hypopnea syndrome (OSAHS) is a serious medical condition characterized by partial or complete cessation of air flow that frequently happens during sleep. It is one of the most common sleep disorders and it is estimated that in the United States, 4% of men and 2% of women who are middle-aged have OSAHS (Young et al., 1993). Historically, it is manifested by snoring, morning headache, gasping for air, witnessed apneas, excessive daytime sleepiness, nocturia, and diaphoresis (Guilleminault, Tilkian, & Dement, 1976). Clinically, it is manifested by obesity, hypersomnolence, high body mass index (BMI), thick neck, macroglossia, and crowded oropharynx (Guilleminault et al., 1976; Katz, Stradling, Slutsky, Zamel, & Hoffstein, 1990; Mallampati et al., 1985). Risk factors are mainly male gender, obesity, older age, and positive family history. Diagnosis of OSAHS is confirmed by sleep study or polysomnography (PSG), during which several physiological activities are monitored and recorded. These include electroencephalography, electrooculography, electrocardiography, electromyography, snoring, respiratory efforts, nasal airflow, and pulse oximeter. The severity of OSAHS is defined based on the Apnea-Hypopnea Index (AHI), which is the number of apnea and hypopnea events per hour of sleep. An Apnea-Hypopnea Index <5, $5 \leq AHI \leq 14$, $15 \leq AHI < 30$, and $AHI \geq 30$ are considered normal, mild, moderate, and severe, respectively. Obstructive sleep apnea hypopnea syndrome is mainly treated with positive airway pressure (PAP), oral appliances (OA), and surgery. Positive airway pressure is the main treatment for obstructive sleep apnea (OSA) and is offered in different modes: continuous PAP (CPAP), automatically adjusted CPAP (APAP), and bilevel PAP (Bi-PAP). The consequences of OSAHS are mainly hypertension, heart attack, stroke, and diabetes mellitus (Young et al., 2008).

NEUROCOGNITIVE FUNCTIONS

Neurocognitive functions are cognitive functions associated with specific pathways or loci within the brain and are affected by different disease processes. Testing specific neurocognitive functions can be used to deduce which areas of the brain are involved when cognitive problems are suspected. Therefore, neurocognitive dysfunction has been the center of attention in many medical conditions and sleep apnea is no exception. Sleep researchers have investigated the link between OSAHS and neurocognitive performance in different ways. Some investigators have evaluated cognitive performance only in untreated OSA patients, whereas

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others have assessed it in OSA patients before and after PAP treatment. Some researchers have contrasted neurocognitive performance after treating OSA patients with different modes of treatments, and finally, a few investigators have assessed cognitive function after CPAP withdrawal.

NEUROCOGNITIVE FUNCTIONS IN UNTREATED OSA PATIENTS

To find out about the association between OSAHS and cognitive function, Blackwell et al. (2011) conducted a cross-sectional clinical trial on 2909 men aged 67 years or older. All participants underwent in-home PSG that showed that 78% had sleep apnea (35% mild, 26% moderate, and 17% severe). Their cognitive functions were evaluated with the Trail Making Test–Part B (Trails B) and Digit Vigilance Test (DVT). Trails B was used to measure attention, sequencing, visual scanning, and executive function and DVT was used to measure vigilance. The researchers found no significant association between cognitive function and the presence or absence of OSA.

Twigg et al. (2010) investigated attention and memory (episodic, semantic, and working) in 60 patients with mild to severe OSA and 60 healthy controls. Healthy subjects were matched for age and education, although their BMI was significantly different. Before undergoing PSG, each participant was evaluated with an extensive battery of cognitive tests (3 h long). On episodic memory, the authors found impaired verbal but intact visual memory in OSA patients, and concluded that these patients have difficulty acquiring new information but no difficulty retaining previously learned memories. Semantic memory testing revealed some impairments, but not to a significant level. The authors found working memory and attention to be unaffected in patients with OSA and showed that memory impairment is not related to severity of OSA. In the end, they concluded that memory impairment might be seen in mild cases of OSA, as well.

Wong, Marshall, Grunstein, Dodd, and Rogers (2008) were interested to know whether sleep deprivation affects neurocognitive functions in OSA patients more than in healthy individuals. To answer this question, they designed a clinical trial to evaluate the effects of 40 h sleep deprivation on both groups. Eight patients with moderate to severe OSA and nine healthy individuals completed this study. All participants had baseline sleep (8 h of bedtime) followed by the period of sleep deprivation during which each participant was evaluated every 2 h. The authors found no difference in performance decrements between OSA patients and healthy controls in the Psychomotor Vigilance Test (PVT). In their trial, patients with OSA did not respond to sleep deprivation differently from healthy controls. This study confirmed that total sleep deprivation led to significant worsening in performance in both groups.

To study the association between sleep apnea and cognitive functions, Spira et al. (2008) conducted a cross-sectional clinical trial in a large group of older women. A total of 448 elderly women (83 years of age, on average) were able to complete the Mini Mental Status Exam and Trails B cognitive function tests. All underwent home PSG. The study showed that there is a strong association between severity of OSA and cognitive impairment, and concluded that OSA is an important risk factor for cognitive impairment in older women.

In another clinical trial, Djonlagic, Saboisky, Carusona, Stickgold, and Malhotra (2012) studied 16 patients with mildly moderate OSA and 15 healthy subjects with similar age and BMI as the control group. All participants were tested for motor skill learning (nondeclarative procedural memory) using the Motor Sequence Task during two sessions, before and after diagnostic PSG. The PSG showed no significant difference in total sleep time, sleep efficiency, or sleep stage distribution between groups, but significant differences in AHI, oxygen nadir, and arousal index. The PVT was applied before each session to control for potential differences in attention and vigilance between groups. The researchers concluded that sleep fragmentation associated with OSA can affect off-line learning improvement and that minimizing arousal from sleep is necessary for optimal memory consolidation. In other words, the study provided evidence that sleep continuity in humans is a necessity for optimal sleep-dependent memory processes.

Are neuropsychological deficits seen in patients with OSAHS related to impaired cerebral blood flow (CBF)? To answer this question, Kiratli, Demir, Volkan-Salanci, Demir, and Sahin (2010) conducted a clinical trial on 20 patients, aged 30–60 years. Sixteen of them had moderate to severe sleep apnea. In the morning after the sleep study, patients underwent brain perfusion scintigraphy and a battery of cognitive function tests including the Wisconsin Card Sorting Test, Verbal Fluency Test, Wechsler Memory Scale-Revised, and a Trail Making Test. Trial investigators found a positive association between arterial oxygen saturation (SaO_2) during sleep and CBF in all regions during the awake period, negative correlation between visual memory and SaO_2 during sleep, decreased CBF in the left frontal and left temporal lobes in OSAHS patients, a positive association of CBF and verbal memory with hypoxemia, and decreased CBF after apneic episodes, which could indicate the impairment of upper airway motor control in OSAHS patients.

NEUROCOGNITIVE FUNCTIONS BEFORE AND AFTER CPAP TREATMENT

Antic et al. (2011) conducted a clinical trial on a group of OSA patients with moderate to severe disease and a control group who were matched for age, sex, and years of education. A total of 141 of 174 participants completed the

trial. Trial investigators evaluated three aspects of cognitive function: verbal memory, executive function, and vigilance, before and after CPAP therapy. In this study, after 3 months of CPAP use, patients showed significant improvement in verbal memory and executive function but not improvement in vigilance.

Orth et al. (2005) studied a group of patients with mild to moderate OSA. They targeted alertness, vigilance, and divided attention in the trial. The authors used neuropsychological tests (Wiener test system and Zimmermann test battery). These tests were performed before and 2 and 42 days after initiating CPAP therapy in patients whose OSA was confirmed with PSG. Testing was performed either between 9 and 11 am or at 4–6 pm according to the circadian rhythm, to represent the daytime periods in which alertness is highest. The trial showed that divided attention and alertness improved significantly during CPAP therapy, whereas vigilance remained unchanged.

Ye, Pien, Ratcliffe, and Weaver (2009) conducted a clinical trial to find out whether there were differences between men and women in terms of OSA manifestation and response to its treatment. In this trial, they assessed 176 participants (152 men and 24 women) with severe OSA at baseline and 3 months after treatment. Subjects had similar age, BMI, and AHI. Investigators used PVT to assess neurobehavioral performance (sustained attention). At baseline, both genders showed poor performance on PVT (with women showing poorer performance). After CPAP therapy, both genders showed significant improvement, whereas the magnitude of improvement did not vary by gender.

Csábi, Várszegi, Sefcsik, and Németh (2012) conducted a clinical trial to determine the effects of CPAP on sleep, neurocognition, and anxiety. They studied 24 patients with sleep apnea in terms of working memory, short- and long-term episodic memory, and executive functions. Patients were evaluated with a battery of neuropsychological tests before and after 2.5 months of using CPAP. With this study, the researchers showed that positive airway pressure treatment restored cognitive function, and in the end they concluded that cognitive dysfunction is partially reversible in OSA patients after CPAP therapy.

NEUROCOGNITIVE FUNCTION IN OSA PATIENTS WHO RECEIVED DIFFERENT MODES OF TREATMENT

Kushida et al. (2011) conducted a randomized, double-blinded, three-arm clinical trial to find out whether flexible APAP (A-Flex) is more efficient than CPAP or APAP-derived optimal pressure for CPAP ($CPAP_{APAP}$). Of 168 patients with moderate to severe sleep apnea, 140 completed this-long term study (6 months). The PVT was evaluated at baseline and after 30, 90, and 180 days. Although there was improvement in vigilance after treating sleep apnea, no significant difference was observed in vigilance improvement across groups.

In an effort to show that impairment in working memory test is local (prefrontal) rather than global, Thomas, Rosen, Stern, Weiss, and Kwong (2005) evaluated 16 patients with moderate to severe OSAS and 16 healthy individual subjects. They used the two-back verbal memory task before and 8 weeks after using CPAP/Bi-PAP. Functional imaging of the brain was performed during the working memory test. They found no dorsolateral prefrontal activation before treatment. The authors also found that after treatment there was no significant change in behavioral performance, persistent lack of prefrontal activation, and partial recovery of posterior parietal activation. They concluded that working memory impairment is associated with a disproportionate impairment of function in the dorsolateral prefrontal cortex.

To show that APAP titration is as effective as manual titration among patients with OSA, McArdle et al. (2010) measured Trails A and B cognitive function tests in their clinical trial as part of baseline measurements. A total of 249 patients with similar age and BMI and diagnosis of moderate to severe OSA participated in the trial. Patients were randomized to three different therapeutic groups: manual titration, automatically titrated in the sleep lab, and automatically titrated at home. Based on the titrations, they were prescribed fixed pressure CPAP to use for 4 weeks. All patients who completed the study among the three groups showed similar improvement in cognitive function.

Lim et al. (2007) conducted a study with randomized placebo-controlled design. Forty-six OSA patients participated in the trial and were assigned to one of the three arms of the study (therapeutic CPAP, supplemental oxygen, or placebo CPAP) for 2 weeks. They were similar in terms of age, BMI, and AHI (all had severe OSA). Before and after the interventions, patients were tested with a battery of neuropsychological tests targeting different cognitive domains including speed of information processing, attention and working memory, executive functioning, alertness and sustained attention, verbal learning and memory, verbal short-term memory and working memory, visuospatial memory, and psychomotor performance. The only domain that showed significant improvement was speed of information processing. The investigators concluded that 2 weeks of intervention was not sufficient to show overall beneficial cognitive effects, compared with placebo CPAP.

In another clinical trial, sustained attention, decision making, and visuomotor coordination were investigated. In this trial, Karimi et al. (2013) used the Attention Network Test (ANT), Compensatory Tracking Task (CTT), and Gothenburg sleep resistance test (Goslin) as tools for evaluating neurocognitive function. Patients underwent overnight ambulatory home polygraphy. Subsequently, those with OSA were treated with CPAP or a mandibular advancement device (MAD), depending on the severity of

OSA at baseline. Patients showed no change in ANT results, a significant improvement in CTT, and some improvement on the Goslin test.

To find out which mode of CPAP (fixed or variable pressure) is preferred by OSA patients, Vennelle et al. (2010) conducted a randomized, blinded, crossover clinical trial on 200 patients with moderate to severe sleep apnea. Each patient underwent 6 weeks of fixed pressure CPAP followed by 6 weeks of variable pressure CPAP, or vice versa. A total of 181 were able to complete the trial. At the end of each 6 weeks of treatment, patients were tested with PVT. Their study showed no difference in vigilance.

In a clinical trial, Barnes et al. (2004) investigated the efficacy of different modes of treatment of sleep apnea. One hundred and fourteen OSA patients with mild to moderate disease participated in this randomized, controlled, crossover trial. Most were middle-aged obese men with normal IQ. Patients underwent 3 months of treatment with CPAP, mandibular advancement splint (MAS), or placebo tablet. A broad range of neuropsychological functions was assessed. The researchers found that both CPAP and MAS were superior to placebo in improving executive cognitive function, and CPAP increased vigilance. They observed no other treatment effects on neurocognitive function.

In a randomized, controlled, crossover clinical trial, Phillips et al. (2013) studied the health outcomes of CPAP use versus oral appliance use. A total of 126 patients with moderate to severe OSA participated in this trial; 108 patients completed therapeutic interventions including CPAP and MAD. In terms of neurobehavioral outcomes, patients were evaluated with a driving simulator before and 1 month after each intervention. Study investigators showed that both MAD and CPAP treatments improved main health outcomes similarly, and that similar effectiveness might be the result of greater efficacy of CPAP being offset by inferior compliance relative to MAD.

To compare the effect of OA with CPAP and placebo on OSA patients, Hoekema et al. (2007) conducted a randomized, controlled, clinical trial on 20 OSA patients and 16 control subjects. The OSA patients had moderate to severe sleep apnea and were similar to control subjects in age. To evaluate attention, OSA patients and the control group were evaluated with a simulated driving test under the same conditions. The OSA patients were randomized into two groups. Ten patients used OA and 10 used CPAP for 2–3 months. At baseline, OSA patients had significantly more lapses of attention than controlled subjects. Both treatments (OA and CPAP) lowered the number of lapses of attention significantly, although there were insignificant differences between treatments. The authors concluded that adequate treatment of sleep apnea will result in considerable improvement of simulated driving in most cases.

To evaluate the effect of OSA treatment on neurocognitive performance, Naismith, Winter, Hickie, and Cistulli (2005) conducted a randomized, controlled, crossover clinical trial. In this trial, 73 patients with moderate to severe sleep apnea participated. They had similar age, BMI, education, and estimated IQ and were divided into two groups. One group (36 patients) was assigned to MAS for 4 weeks followed by no treatment for another 4 weeks. Second group (37 patients) was assigned to no treatment for 4 weeks followed by MAS for another 4 weeks. Patients were evaluated at baseline and at weeks 4 and 8. Targeted neuropsychological domains were speed and vigilance, attention and working memory, verbal learning and memory, visuospatial functioning, and executive functioning, among which only vigilance and psychomotor speed showed improvement.

NEUROCOGNITIVE FUNCTIONS AFTER CPAP WITHDRAWAL

In contrast to other investigators, Kohler et al. (2011) conducted a randomized clinical trial to evaluate psychomotor performance before and after withdrawing CPAP use for 2 weeks. Forty patients completed the study in which 20 patients received sub-therapeutic CPAP and 20 received therapeutic CPAP. Investigators assessed divided attention and behavioral alertness by a divided attention driving simulator test and PVT, respectively. They conducted assessments in the evening at baseline and at 2 weeks. The study showed no significant decline in psychomotor function within 2 weeks of CPAP withdrawal.

Yang et al. (2006) investigated the effect of CPAP withdrawal on 20 patients who had been using CPAP for at least 12 months before participation. They conducted PVT, the serial additional and subtraction task, the digit symbol substitution task, and probed memory recall to assess attention and cognitive processing. These assessments were done before withdrawing CPAP and on the morning after (acute) and 7 days after (short-term) withdrawal. Among neurobehavioral measurements, only attention was impaired. Therefore, they concluded that apparently most cognitive functions are not affected by short-term CPAP withdrawal in patients receiving long-term therapy.

DOES TREATING SLEEP APNEA IMPROVE NEUROCOGNITIVE FUNCTION?

To quantify the effect of CPAP treatment on neurocognitive function, Kylstra, Aaronson, Hofman, and Schmand (2013) carried out a meta-analysis. They searched the literature for all clinical trials published from January 1990 through July 2012 that were conducted to assess the effect of CPAP treatment on neuropsychological function. The authors searched for randomized, controlled trials in which patients' OSA was confirmed by PSG, a CPAP treatment compliance report was available, and at least one standardized neuropsychological test was done in the study. The literature search

resulted in 13 studies. In total, neurocognitive test results of 533 patients who had mild to severe OSA and were treated with CPAP and 497 OSA patients as the control group were included in this meta-analysis. Patients were middle-aged (average age, 50.5 years), obese (average BMI, 30.4 kg/m^2) and CPAP compliant (average CPAP use, 4.5 h/night). A wide range of cognitive functions including vigilance, memory, attention, processing speed, working memory, verbal fluency and visuo-construction were evaluated. In the end, the study investigators concluded that the effect of CPAP on cognition is small and limited to attention.

To examine memory performance in patients with OSA, Wallace and Bucks (2013) conducted a meta-analysis. After setting inclusion and exclusion criteria, they searched the database, which resulted in 2517 studies from which 42 met the criteria and were reviewed. Altogether, 2294 adults with untreated OSA and 1364 healthy controls were studied in these trials. Authors concluded that based on the results of the meta-analyses, OSA patients are significantly impaired compared with healthy controls on verbal episodic memory (immediate recall, delayed recall, learning, and recognition) and visuospatial episodic memory (immediate and delayed recall), but not visual immediate recall or visuospatial learning. When patients were compared with normal subjects, negative effects of OSA were found only in verbal immediate and delayed recall.

To investigate the long-term neurocognitive benefits of CPAP therapy, Kushida et al. (2012) conducted a large, randomized, double-blind, controlled clinical trial. Of 1516 participants, 1224 were diagnosed with sleep apnea and 1098 were randomized to either active CPAP (556) or sham CPAP (542). Study evaluations were done at three points during the study: baseline (before starting CPAP) and 2 and 6 months after using CPAP. Participants were similar in terms of gender distribution, race distribution, severity of OSA (mild, moderate, and severe), age, marital status, BMI, and education. The three primary neurocognitive outcomes were attention and psychomotor function (A/P), verbal learning and memory (L/M), and executive and frontal lobe function (E/F). Except for some improvement in the E/F domain of neurocognition after 2 months of CPAP therapy, analyses showed no improvement in A/P or L/M domains of neurocognitive performance after 2 or 6 months or E/F domain after 6 months of CPAP use. Because the improvement in neurocognitive domains was mild, transient, and limited, the investigators concluded that there might be a complex relationship between OSA and neurocognitive performance.

CONCLUSION

As we have seen, there is no universal agreement among authors regarding the effect of sleep apnea on neurocognitive functions. Overall, it is suggested that there is a relationship between untreated sleep apnea and cognitive impairment, but that is as far as the data take us. There are several factors at play. First of all, there might be a protective mechanism. Second, many of the studies looked at cognition but did not take cognitive effects as a primary end point. Third, there was inconsistency in both diagnosis and treatment of sleep apnea, with only a few studies actually using objective measures of treatment efficacy to exclude sleep apnea treatment failures from the database. This in turn is complicated by our evolving ability to measure CPAP compliance as well as ongoing self-monitoring of apnea control by the devices themselves. Fourth, most studies did not have a large patient population. Fifth, there were variations between studies in terms of the severity of patients' OSA, type of sleep study (in lab versus home testing), age of patients, presence or absence of mental disorders (e.g., depression), use of different neurocognitive tests, inclusion of a control group, and so forth. Finally, there is the question of what aspects of cognition are important. In measuring cognitive outcomes, we measure what we can measure, which is not necessarily the same as what is impactful to the patient's quality of life and health. This is an important question not only for the individual patient, but also for society as a whole. Currently, United States Federal authorities are trying to determine when a sleep apnea patient—whether a commercial airline pilot, a long-distance heavy truck operator, or even an airport security screener—is impaired and when he or she is not capable of safely doing the job. These data suggest that the current standards of CPAP compliance and maintenance of wakefulness testing need to be augmented by some sort of cognitive testing. At this time, we do not know conclusively what or when to test.

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Chapter 8

Adipose Tissue in Sleep Apnea: Effects of Hypoxia and Inflammation

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INTRODUCTION

Obstructive sleep apnea (OSA) and obesity are often associated, and they share possible pathogenetic mechanisms (Bonsignore, McNicholas, Montserrat, & Eckel, 2012). Both conditions are characterized by hypoxia and inflammation. In OSA, intermittent hypoxia occurs during sleep and causes inflammatory activation (Kent, Ryan, & McNicholas, 2011), oxidative stress (Lavie & Lavie, 2009), insulin resistance (Iiyori et al., 2007; Louis & Punjabi, 2009), and autonomic dysfunction (Chalacheva, Thum, Yokoe, O'Donnell, & Khoo, 2013; Prabhakar, Kumar, & Peng, 2012). In visceral obesity, a complex metabolic picture develops as a consequence of increased nutrient availability and inflammation (Schenk, Saberi, & Olefsky, 2008). Hypoxia may occur in enlarged adipocytes and is associated with release of proinflammatory adipokines (Trayhurn, 2013), insulin resistance (Shoelson, Lee, & Goldfine, 2006), and recruitment of inflammatory cells (Lumeng, Bodzin, & Saltiel, 2007).

The frequent association of OSA and visceral obesity, on one hand, makes it difficult to assess their independent role in cardiometabolic disorders; on the other hand, it has stimulated recent research on the role of intermittent hypoxia in adipose tissue of obese OSA patients. Animal models of OSA are available (Jun & Polotsky, 2007), with the advantage that the effects of intermittent hypoxia can be studied in lean and obese animals (Lévy, Bonsignore, & Eckel, 2009). Moreover, direct measurement of oxygen partial pressures (PO_2) can provide information on the actual hypoxic exposure in different tissues in vivo, including adipose tissue (Almendros et al., 2011; Reinke, Bevans-Fonti, Drager, Shin, & Polotsky, 2011). The steady research advancement in OSA and obesity will hopefully suggest new therapeutic approaches in both fields.

This chapter summarizes recent data on (1) the effects of hypoxia and inflammation in adipose tissue and (2) metabolic changes in animal models exposed to continuous or intermittent hypoxia. Finally, the clinical implications of basic research findings will be discussed.

HYPOXIA AND INFLAMMATION IN ADIPOSE TISSUE

Adipose tissue was once considered a depot of fat with low metabolic activity, but in the past decades research on the mechanisms of obesity has completely changed such paradigms. Adipose tissue is metabolically active, but differences exist according to its type and distribution (see Bonsignore et al., 2012 for a review). White adipose tissue (WAT) accumulates mainly in visceral and subcutaneous depots. Visceral fat is metabolically more active than subcutaneous fat and its accumulation is linked to increased cardiovascular risk, suggesting the opportunity to classify patients according to obesity phenotypes (Karelis, St-Pierre, Conus, Rabasa-Lhoret, & Poehlman, 2004).

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Besides WAT, brown adipose tissue (BAT), once considered absent in adult humans, has been recently shown to persist beyond the first year of life and be metabolically active. BAT activity can be induced by cold exposure in healthy subjects (van Marken Lichtenbelt et al., 2009) causing weight loss (Yoneshiro et al., 2013). BAT decreases with age (Yoneshiro et al., 2011) and in overweight/obesity (Vijgen et al., 2011), and increases after weight loss (Vijgen et al., 2012), suggesting that BAT exerts a relevant role in the maintenance of a healthy metabolic profile and body weight (Yoneshiro et al., 2011). BAT is increasingly studied because it promotes thermogenesis and increased metabolic rate (Lee, Swarbrick, & Ho, 2013), and possibly exerts endocrine functions (Villarroya, Cereijo, & Villarroya, 2013). Brown-like adipocytes ("brite" adipocytes) are found in WAT and may also play a role in metabolism (Rosenwald, Perdikari, Rülicke, & Wolfrum, 2013).

Visceral obesity is a state of low-grade inflammation (Hotamisligil, 2006), and adipose tissue undergoes profound remodeling during its expansion in obese individuals (Sun, Kusminski, & Scherer, 2011). Macrophages infiltrate obese adipose tissue in response to different mechanisms (i.e., removal of dead adipocytes, chemotactic attraction, hypoxia, and increased fatty acid flux) (Sun et al., 2011). In addition, adipose tissue macrophages in obesity switch from the anti-inflammatory M2 to the proinflammatory M1 phenotype (Lumeng & Saltiel, 2011). This process is associated with a profound disturbance in the activity of immune cells in fat, and activation of multiple proinflammatory pathways in several tissues, including central nervous system, pancreas, liver, and skeletal muscle (Lumeng & Saltiel, 2011).

It was hypothesized that hypertrophic white adipocytes could become hypoxic due to an increased distance between cell and capillary, and hypoxia might contribute to metabolic dysfunction in obesity (Trayhurn, Wang, & Wood, 2008). Insulin resistance, decreased production of adiponectin, and release of reactive oxygen species were shown to occur in adipocytes in vitro in response to continuous hypoxia (Regazzetti et al., 2009). Most of these in vitro studies in adipocytes used very extreme exposure conditions, with O_2 concentration ranging from 21% (hyperoxic compared with in vivo conditions), to 1% (profound hypoxia). More recent in vitro studies using physiological O_2 concentrations confirmed progressive changes in adipokine transcription and release when adipocytes were exposed to increasing levels of hypoxia (Wood, Stezhka, & Trayhurn, 2011).

In 2007, direct measurements of tissue PO_2 were obtained in mice with normal arterial O_2 saturation while breathing room air. Tissue hypoxia was shown in visceral fat in obese mice, while normoxia was found in skeletal muscle (Ye, Gao, Yin, & He, 2007), lung, kidney, or heart (Hosogai et al., 2007). Adipose tissue hypoxia in obese animals was secondary to decreased perfusion of fat (Hosogai et al., 2007).

The hypoxia-inducible factor 1 alpha (HIF-1α) is the main player in the cellular response to hypoxia (Semenza, 1998). Expression of HIF-1α and HIF-1α–dependent genes, such as the glucose transporter GLUT-1, glycolytic enzymes, and vascular endothelial growth factor (VEGF), was increased in animals on a high-fat diet (Ye et al., 2007). In addition, hypoxia increased the expression of inflammatory cytokines such as interleukin (IL)-1, IL-6, monocyte chemoattractant protein-1, and tumor necrosis factor α (Hosogai et al., 2007; Ye et al., 2007) and decreased the expression of adiponectin, a protective metabolic factor synthesized by adipose tissue (Hosogai et al., 2007; Ye et al., 2007). In agreement with these experimental results, Pasarica and associates documented a lower PO_2 in subcutaneous adipose tissue of obese compared with lean humans but failed to show activation of HIF-1α–dependent genes (Pasarica et al., 2010). The capillary rarefaction in obese adipose tissue was highly suggestive of inadequate capillary growth as the main mechanism of fat hypoxia in obese humans (Pasarica et al., 2010).

Since VEGF is likely involved in angiogenesis in adipose tissue and can be activated by the HIF-1 pathway, transgenic mouse models have been used to explore the roles of HIF-1α and VEGF in obesity (Table 8.1). Most studies using HIF-1 antisense oligonucleotides, or a dominant negative HIF-1α gene, reported weight loss associated with unchanged food intake and increased metabolic rate, and improvement in metabolic variables in obese animals (Jiang et al., 2011; Park et al., 2012; Shin et al., 2012; Sun, Halberg, Khan, Magalang, & Scherer, 2013; Zhang et al., 2010). Conversely, studies inducing selective changes in VEGF expression in adipose tissue of mice on a high-fat diet reported worsening of obesity and metabolic abnormalities during VEGF inhibition (Sun & Feinberg, 2012; Sung et al., 2013) and opposite changes during VEGF overexpression (Elias et al., 2012; Sun & Feinberg, 2012; Sung et al., 2013). Interestingly, overexpression of VEGF was associated with increased blood vessel counts in both WAT and BAT, but modulation of BAT seemed physiologically relevant since reduced weight gain appeared related to increased metabolic rate (Elias et al., 2012; Sun & Feinberg, 2012; Sung et al., 2013). One study reported that VEGF overexpression caused "browning" of WAT and reduced adipose tissue inflammation and remodeling (Sun & Feinberg, 2012). VEGF could also play a positive role in modulating the macrophage function in adipose tissue toward the anti-inflammatory M2 phenotype (Elias, Franckhauser, & Bosch, 2013). An interesting hypothesis suggests that early or late modulation of angiogenesis in the natural history of obesity might also affect the response of WAT (Yilmaz & Hotamisligil, 2013). In summary, different results were obtained by HIF-1α and VEGF modulation in adipose tissue. The picture is complicated by the fact that HIF-1α in adipose tissue might be regulated not only

TABLE 8.1 Summary of the Experimental Studies on the Effects of Hypoxia-Inducible Factor (HIF) and Vascular Endothelial Growth Factor (VEGF) Inhibition or Overexpression in Obesity

Authors	Methodology	Tissue mRNA Expression	Results
Zhang et al. (2010)	Transgenic mice with adipose tissue-selective dnHIF-1α during HFD	dnHIF-1α in BAT, subcutaneous and epididymal WAT	↑weight gain, ↑IR, ↓angiogenesis in BAT but not in WAT
Jiang et al. (2011)	Transgenic mice with adipocyte-specific HIF1α or ARNT-KO during HFD	Reduced HIF-1α in BAT and WAT	↓weight gain, ↓IR, ↑adiponectin, Unchanged food intake, ↑ metabolic rate, ↓RER, ↓fat mass
Park et al. (2012)	Mice treated with HIF1α ASO during HFD	Not assessed	↓weight gain, ↓retroperitoneal and subcutaneous fat mass, ↓plasma lipid concentrations, ↓liver weight, ↓adipocyte size
Shin et al. (2012)	Mice treated with HIF1α ASO during HFD	Reduced HIF-1α in liver, BAT, epididymal and omental WAT	↓weight gain, ↓IR = food intake, ↑metabolic rate, ↓RER, ↓fat mass in all depots, ↑liver weight (glycogen synthesis)
Sun et al. (2013)	Transgenic mice with dnHIF1α, PX-478 (HIF-1α selective inhibitor) during HFD	dnHIF-1α in BAT, subcutaneous and epididymal WAT; ↓HIF-1α in the same tissues after PX-478	↓weight gain, ↓IR, ↑adiponectin, Unchanged food intake, ↑ metabolic rate, ↓RER, ↓fat mass in both models
Sun et al. (2012)	Transgenic mice with adipose tissue overexpression of VEGF-A during HFD; anti-VEGF monoclonal Ab Mcr84 to mice before and during HFD		*VEGF overexpression*: ↓weight gain, ↑WAT vascularization, ↓IR, ↑food intake, ↑RER, "browning" of WAT, ↓AT inflammation and fibrosis. *VEGF inhibition*: ↑weight gain, ↑IR, worsening of metabolic profile; ↑WAT inflammation
Elias et al. (2012)	Transgenic mice with adipose tissue overexpression of VEGF-A during HFD	VEGF-A ↑in different WAT depots and interscapular BAT	↓weight gain, ↑WAT and BAT vascularization, ↓IR, Unchanged food intake, ↑BAT thermogenesis and energy expenditure, ↓ hepatic steatosis, ↓AT inflammation with predominance of M2 macrophages
Sung et al. (2013)	Transgenic mice with adipose tissue-selective: a) VEGF-A deletion; b) doxycyclin-induced VEGF-A overexpression after induction of HFD-obesity		*VEGF deletion*: ↑weight gain, ↓WAT and BAT vascularization; ↑IR, worsening of metabolic profile; ↑WAT inflammation *VEGF overexpression* in HFD-induced obesity: ↓weight, ↑WAT and BAT vascularization, ↓IR, Unchanged food intake and energy expenditure, ↓hepatic steatosis, ↓AT inflammation

Abbreviations: dnHIF-1α: dominant negative hypoxia inducible factor 1α gene; HFD: high fat diet; BAT: brown adipose tissue; WAT: white adipose tissue; IR: insulin resistance; ARNT-KO: aryl hydrocarbon nuclear translocator (HIF-1beta) knock-out; ASO: antisense oligonucleotide; RER: respiratory exchange ratio; AT: adipose tissue.

by hypoxia but also by other important metabolic signals, including insulin (He et al., 2011). More studies are needed in order to translate the results of experimental studies into clinically applicable treatment strategies.

Studies in humans have provided some intriguing results. Goossens and coworkers continuously monitored adipose tissue blood flow and PO_2 in lean and obese humans (Goossens et al., 2011). Obese subjects showed a blunted increase in blood flow and PO_2 in adipose tissue in response to ingestion of glucose, confirming previous findings (Sotornik et al., 2012). However, PO_2 in adipose tissue of obese subjects was high despite decreased blood flow, suggesting that a low metabolic rate in fat was associated with insufficient capillarization, insulin resistance, and inflammation (Goossens et al., 2011). Similar conclusions were reached by a subsequent study from another group (Hodson, Humphreys, Karpe, & Frayn, 2013). The implications of these two studies are that reduced vascularization of fat in obese humans could result from decreased angiogenetic stimulation associated with low metabolic rate, rather than reflect insufficient vessel growth during fat expansion (Corvera & Czech, 2011). The reason for the discrepancies between experimental and human studies is still a matter of debate. A possible explanation of the different results is that insufficient vascularization of adipose tissue in animal models might be secondary to massive obesity developing over a short period of time, different than the slow process typical of human obesity (Goossens & Blaak, 2012).

In summary, recent research in the obesity field has provided new data on the role of hypoxia-dependent pathways in adipose tissue of lean and obese subjects. However, many questions remain open, and the current state of knowledge does not allow one to predict the role played by intermittent hypoxia, such as in OSA, in the complex disturbance of adipose tissue occurring in obesity.

EFFECTS OF INTERMITTENT OR CONTINUOUS HYPOXIA

The studies on adipose tissue PO_2 described in the previous section were conducted in animals or subjects breathing room air. Subjects with OSA are exposed to intermittent asphyxia (i.e., hypoxia and hypercapnia) caused by upper airway closure during sleep. Therefore, in adipose tissue of obese OSA patients, the effects of nocturnal apneas are superimposed to those of obesity.

The effects of intermittent and continuous hypoxia have been studied in cells in vitro and animal models. HeLa cells exposed to intermittent hypoxia showed activation of the proinflammatory NF-κB–dependent cascade and little activation of the adaptive HIF-1 pathway (Ryan, Taylor, & McNicholas, 2005); conversely, cell exposure to continuous hypoxia caused HIF-1 rather than NF-κB activation (Ryan et al., 2005). These data suggested that inflammatory activation, rather than the adaptive response to hypoxia, was the hallmark of OSA.

However, the effects of intermittent hypoxia in vivo are more complex. While inflammatory activation occurs in OSA patients (Ryan, Taylor, & McNicholas, 2009) and likely contributes to the pathogenesis of endothelial dysfunction and early atherosclerotic lesions (Drager, Polotsky, & Lorenzi-Filho, 2011), the HIF-1 pathway also appears to be involved in the response to intermittent hypoxia, especially in the carotid body (Prabhakar, 2013), for regulation of blood pressure and ventilation (Peng et al., 2006), and in the modulation of metabolic responses (Li et al., 2006). Interactions between the NF-κB and HIF-1 pathways have been reported (Rius et al., 2008), indicating a high degree of complexity in the integration of inflammatory and hypoxic responses. In addition, a protective role of p50 HIF-1 subunit has been shown in the development of atherosclerosis during exposure to chronic intermittent hypoxia in APO-E knock-out mice (Fang et al., 2012). Therefore, more studies are needed to identify which of the multiple components of the HIF-1 pathway might be involved in the complex pathophysiology of intermittent hypoxia and their respective roles (Sun & Feinberg, 2012).

Experimental models greatly helped to understand the metabolic effects of intermittent hypoxia. In mice and rats, exposure to intermittent hypoxia during the daytime (sleep period for rodents) has been extensively used to reproduce the oscillations in arterial oxygen saturation (SaO_2) seen in OSA patients during sleep (Jun & Polotsky, 2009; Lee, Woodske, Zou, & O'Donnell, 2009). Another model used upper airway closure to cause OSA in anesthetized rats (Farré et al., 2007).

The extensive literature on the effects of intermittent hypoxia on several metabolic variables in mice has been summarized in recent reviews (Bonsignore & Eckel, 2009; Bonsignore et al., 2012; Drager, Jun, & Polotsky, 2010; Farré, Montserrat, & Navajas, 2008; Jun & Polotsky, 2009; Levy et al., 2009). Briefly, intermittent hypoxia worsens insulin sensitivity in lean (Iiyori et al., 2007) and obese (Polotsky et al., 2003) mice, but its effects appear reversible, at least in part, on cessation of exposure (Polak et al., 2013). Plasma lipids are also affected in both lean (Li, Thorne, et al., 2005) and obese (Li, Grigoryev, et al., 2005) mice. During intermittent hypoxia triglyceride levels are increased due to inhibition of lipoprotein lipase in different adipose tissue depots including BAT, but the mechanism is still incompletely understood (Jun et al., 2012; Yao et al., 2013). Finally, in mice on a high-fat diet, chronic intermittent hypoxia caused liver damage (Savransky et al., 2007) and accelerated atherosclerosis (Savransky et al., 2008).

A contribution to our understanding of the interplay between hypoxia and metabolism can come from studies investigating the effects of *continuous* hypoxia on adipose tissue in the mouse model (van den Borst et al., 2013). Lean

mice chronically exposed to 8% O_2 for 3 weeks showed weight loss, reduced adipocyte size and adipose tissue mass. Inflammation in adipose tissue decreased compared with 21% O_2 exposure. Expression of VEGF-A and other HIF-1–dependent genes increased in both visceral and subcutaneous fat, while adiponectin expression increased only in visceral fat (van den Borst et al., 2013). Overall, the picture was very similar to the effects of enhanced metabolic rate seen in studies with VEGF overexpression (Table 8.1); indeed, expression of uncoupling protein-1 (UCP-1), a mediator of BAT-induced thermogenesis, increased in both visceral and subcutaneous fat (van den Borst et al., 2013). These results underline the differences in behavior of adipose tissue according to the pattern of exposure to hypoxia, and point to modulation of BAT activity as a possible player not only in obesity but also in hypoxic conditions.

Some studies investigated adipose tissue and metabolic function during animal exposure to *intermittent* hypoxia. Two studies in rats reported decreased body weight and BAT weight during exposure to chronic intermittent hypoxia; unfortunately, UCP-1 levels were not measured (Martinez et al., 2010; Martinez, Vasconcellos, de Oliveira, & Konrad, 2008). A later study from the same group found decreased UCP-1 expression and adiponectin levels in BAT of rats exposed to hypoxia, and concluded that hypoxia may interfere with normal energy control mechanisms (Fiori et al., 2013). Results may be affected by species differences, since in lean APO-E mice exposed to intermittent hypoxia for 6 weeks, it was found that visceral WAT underwent remodeling (i.e., decreased adipocyte size, increased UCP-1 expression, inflammatory activation, and development of insulin resistance) (Poulain et al., 2014). Moreover, the effects of intermittent hypoxia may differ between lean and obese animals, as indicated by a study that showed minimal metabolic derangements in lean compared with high-fat diet obese mice (Drager, Li, et al., 2011). Unfortunately, this latter study did not examine adipose tissue characteristics. Overall, the results obtained in animal models of chronic intermittent hypoxia are still unclear, and future studies will hopefully clarify the role of BAT or of "browning" of WAT in the metabolic response to OSA.

The effects of intermittent hypoxia on tissue PO_2 have been assessed in adipose tissue and other organs, similar to the studies in adipose tissue of obese animals and humans described in the previous section. Almendros and colleagues used the OSA and intermittent hypoxia models to assess acute changes in PO_2 in omental fat, brain, and skeletal muscle in nonobese rats (Almendros et al., 2011). Oscillations in PO_2 during intermittent hypoxia were smaller in fat compared with those found in skeletal muscle or brain, irrespective of protocol used (Almendros et al., 2011). Similarly, Reinke and coworkers tested the effects of different exposures to intermittent or sustained hypoxia on tissue PO_2 in lean and obese mice (Reinke et al., 2011) and also found large oscillations in liver and muscle PO_2 during intermittent hypoxia, while epididymal fat showed decreased PO_2 with much smaller oscillations compared with liver or muscle. Interestingly, during exposure to intermittent hypoxia obese mice showed more severe fall in SaO_2 compared with lean mice, but tissue PO_2 did not differ between lean and obese mice (Reinke et al., 2011). These results, obtained in acute studies, are hard to interpret but suggest a possible role of modulation of blood flow in adipose tissue microcirculation that deserves further study.

Finally, analysis of the transcriptional pattern (transcriptome) of visceral adipose tissue may provide additional information on the response to intermittent hypoxia in fat. Analysis of the transcriptome of visceral fat during 13 days of exposure to intermittent hypoxia in lean mice revealed perturbations of metabolic processes, mitochondrial function and increased oxidative stress, associated with increased plasma cholesterol and triglycerides, and evidence of oxidative stress in adipose tissue (Gharib et al., 2012). Visceral fat transcriptome was also assessed in a small group of obese humans with and without OSA. Predominant activation of the inflammatory NF-κB pathway and deactivation of peroxisome proliferator–activated receptor signaling was found in OSA compared with non-OSA subjects (Gharib, Hayes, Rosen, & Patel, 2013). These data are of great interest, but the picture is still far from being complete. In particular, some of the differences between the animal and human data described here might be due to different amounts of body fat between models under study (i.e., data from obese mice exposed to intermittent hypoxia are lacking).

CLINICAL IMPLICATIONS

Basic research is rapidly growing in both the obesity and OSA fields and can provide new insights to be tested on the clinical ground. A clear message of the studies discussed so far is that obesity is a major factor, and the effects of intermittent hypoxia on metabolism appear amplified especially in obese subjects. At least two recent clinical studies have reexamined the role of OSA on glucose metabolism in nonobese subjects (Borel et al., 2013; Pamidi et al., 2012). Pamidi and coworkers reported insulin resistance in young lean otherwise healthy men with OSA and very mild nocturnal hypoxemia, suggesting a role of sleep fragmentation on glucose metabolism. Borel and coworkers studied 38 non-obese OSA patients (body mass index $< 30\,kg/m^2$) referred for sleep studies, and found insulin resistance and deteriorated cardiometabolic profile in patients with increased waist circumference, a marker of visceral adipose tissue accumulation. Mean nocturnal oxygen saturation inversely correlated with waist circumference, but was the only variable associated with insulin resistance in multivariate analysis. Therefore, OSA and insulin resistance appear causally related even in non-obese patients.

The clinical application of the results on HIF-1α or VEGF modulation in adipose tissue will have to wait until more data are available. Overexpression of VEGF to treat obesity might be difficult to apply clinically, since the positive effects documented in animal models (Table 8.1) could be counteracted by facilitation of cancer progression, especially during intermittent hypoxia (Almendros et al., 2012).

The possibility that BAT is involved in the response to intermittent hypoxia is very interesting. In this context, the experimental findings of decreased UCP-1 transcription in response to intermittent hypoxia (Fiori et al., 2013) suggest an additional dysfunctional factor which might affect adipose tissue in OSA patients. A recent study found that among patients with visceral obesity undergoing a lifestyle intervention program, those who also had OSA lost less weight than patients without OSA (Borel et al., 2012), but BAT was not assessed. Careful studies on the metabolic response to intermittent hypoxia in different adipose tissue types and depots are needed.

Lastly, some recent reports highlight the detrimental effect of sleep deprivation on metabolic derangements in OSA patients (Broussard & Brady, 2010; Cizza et al., 2013; Kim et al., 2013). OSA patients mostly experience sleep fragmentation rather than deprivation, and knowledge on the latter topic is still inadequate. Nevertheless, OSA patients sleeping less than 5 h/night showed a much higher risk for visceral obesity compared with patients sleeping longer than 7 h (Kim et al., 2013). Therefore, the amount of sleep and its quality are also important areas for further clinical investigation on the relationship between OSA and obesity.

CONCLUSIONS

This chapter summarized recent advances in research on the pathophysiology of metabolic alterations in obesity and OSA by focusing on hypoxia and inflammation. Some new areas appear potentially useful to develop new treatments for obesity, and available data on the effects of intermittent hypoxia were discussed. Weight loss remains the most promising target in the long-term management of obesity and OSA, but OSA could impair the response to obesity treatment.

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Chapter 9

Exercise, Diet, and Obese Adolescents: Association with Sleep Deprivation

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SLEEP HABITS IN ADOLESCENTS

Sleeping an adequate number of hours is an important part of a healthy lifestyle. In various age groups from infancy to adolescence, a large number of studies have demonstrated a high prevalence of sleep disorders associated with a great amount of inadequate sleep hygiene practices including irregularity of schedule and napping, habitual use of sleep-disturbing substances such as alcohol, caffeine, or nicotine, and engaging in physically activating, emotionally upsetting, or mentally stimulating activities (watching television, reading, listening to music, or using the computer, among others), especially in the period preceding bedtime (Medicine, 2005). These sleep disturbances have medical, psychological, and social consequences, such as daytime sleepiness (Carskadon, Vieira, & Acebo, 1993; Carskadon, Wolfson, Acebo, Tzischinsky, & Seifer, 1998; Gau & Soong, 1995), poor school performance, behavioral problems (Dahl & Lewin, 2002) and emotional health concerns (Dahl & Lewin, 2002; Ohayon, Roberts, Zulley, Smirne, & Priest, 2000).

Sleep duration or total sleep time typically refers to the total amount of sleep obtained either during the nocturnal sleep episode or across the 24-h period. Several studies show that sleep duration declines considerably from the newborn period to late adolescence, but substantial individual variability remains at all ages. Sometimes a common problem is that parents think that children do not get enough hours of sleep for their age and tend to overestimate children's sleep requirements (Ferber, 1990; Largo & Hunziker, 1984). This is a problem because if the time children spend in bed exceeds their actual sleep need, they may struggle at bedtime, awaken during the night, or awaken too early in the morning. An effective approach to improving these sleep problems is to adjust the time in bed to the real sleep requirement for each age range. Indeed, the average number of hours of sleep that a child (6–13 years) needs is 10–13 h, compared with 14–16 h required by an infant (0–6 years) (Iglowstein, Jenni, Molinari, & Largo, 2003). During adolescence (13–19 years), the number of hours of sleep required continues to decrease, with the average being approximately 8–9 h each night (Strauch & Meier, 1988; Yarcheski & Mahon, 1994). Moreover, in adolescence a sleep pattern characterized mainly by a delay of the sleep period (adolescents tend to stay up later at night and sleep later in the morning) is characteristic and thus shows an age-related increase in eveningness circadian preference. The circadian phase delay of the sleep period is more important on weekends than on weekdays. Although most adolescents go to bed before 2 am on weekdays, a low percentage does during weekends, when most teenagers go to bed between 2 and 5 am and a small percentage go to bed later than 5 am (Vela-Bueno, Fernandeez-Mendoza, & Olavarrieta-Bernardino, 2009). This usually happens because on weekdays the timing of the sleep period is highly determined by early wake times mandated by the school schedule and by greater parental control over bedtime than on weekends. Because of this, there is a tendency to extend sleep during weekends, and this aspect is also attributed to psychosocial factors on weekends.

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According to the criterion of the National Sleep Foundation in America for the adolescent population, less than 8 h/night is defined as insufficient sleep (Lund, Reider, Whiting, & Prichard, 2010); however, 9 h/night is considered an optimal sleep duration at this age (Carskadon & Acebo, 2002). However, the data vary according to different countries. Whereas in European adolescents the average duration of daily sleep is around 8 h in both sexes (Garaulet, Ortega, et al., 2011), these results are higher than data obtained in Asian countries such as China (Liu, Zhao, Jia, & Buysse, 2008), India (Gupta et al., 2008), and South Africa (Reid, Maldonado, & Baker, 2002) (ranging from 7.1 to 7.8 h). The decreased sleep time seen in Chinese adolescents parallels findings reported for adolescents in the United States (Carskadon & Acebo, 2002). All of these studies show that the adolescents in most countries have insufficient sleep duration. This fact has pathological consequences that will be discussed in the next sections.

Different Factors in Sleep Duration and Quality

Although many different aspects may be involved in sleep duration, such as cultural factors and social behaviors, other, more endogenous factors such as *genetic factors* may be also implicated. Indeed, it has been demonstrated that several clock genes are related to the duration of sleep or to the individual chronotype (eveningness or morningness). This is the case, for example, of some single nucleotide polymorphisms (SNPs) in Circadian Locomotor Output Cycles Kaput (*CLOCK),* an essential element of the positive regulatory arm in the human biological clock; for example, genetic variants in *CLOCK* 3111T/C, specifically carriers of the minor C allele, had: (1) shorter sleep duration, (2) delayed breakfast time, (3) evening preference, and (4) less compliance with a Mediterranean Diet pattern, compared with TT homozygotes (Garaulet, Sanchez-Moreno, et al., 2011). A further studied performed by our group also demonstrated that C carriers of *CLOCK* 3111T/C displayed a less robust circadian rhythm than TT and a delayed acrophase that characterizes evening-type subjects (Bandin et al., 2013). We also found highly consistent associations between morning/evening questionnaires across the different genotype categories at *SIRT1* and *CLOCK* loci. Subjects carrying minor alleles at *SIRT1* and *CLOCK loci* were more evening type than homozygotes for both major alleles (Garaulet et al., 2012). Other SNPs, such as those from the *CKIΔ*, *PER2*, or *PER3*, have been related to different disturbances in sleep such as advanced or delayed sleep phase disorders (Toh, 2008). More specifically, in adolescents it has been described that a *PER2* gene variation is associated with alcohol consumption in interaction with sleep problems among Swedish adolescent boys (Comasco et al., 2010).

Moreover, it has been demonstrated that sleep patterns and quality differed between *adolescents born preterm and term*; indeed, adolescents born preterm demonstrated significantly earlier bed and wake times and sleep midpoints (approximately 22 min after adjusting for demographic and psychosocial factors) by actigraphy. They also had significantly fewer arousals and reported being more rested and alert in the morning, as well as less sleepy and fatigued. These findings support a growing body of evidence that *perinatal factors* may influence sleep phenotypes later in life. These factors may reflect developmental influences, as well as the influence of parenting styles on children's sleep (Hibbs et al., 2013).

Social Jet Lag

Another relevant aspect to be considered in adolescence is the permanent social jet lag experienced by a number of adolescents, which results in chronic sleep loss. This concept refers to the discrepancies between social and biological timing. Social (e.g., school and work) schedules interfere considerably with individual sleep preferences in most of the population. Late chronotypes (evening type) show the largest differences in sleep timing between work and free days, leading to a considerable sleep debt on work days, for which they compensate on free days. The discrepancy between work and free days, between social and biological time, can be described as social jet lag (Wittmann, Dinich, Merrow, & Roenneberg, 2006). Among adolescents, some studies have demonstrated that social jet lag is also more frequent among evening types. Older adolescents and evening-oriented adolescents claimed later rising time and bedtime, shorter sleep length on weekdays, but longer sleep duration on weekends and greater social jetlag. Epidemiological studies have demonstrated that greater social jet lag is highly related to obesity (Collado Mateo, Diaz-Morales, Escribano Barreno, Delgado Prieto, & Randler, 2012). Results from a large-scale epidemiological study, have shown that beyond sleep duration, social jet lag is associated with increased body mass index (BMI). Indeed, living "against the clock" may be a factor contributing to the epidemic of obesity.

RELATIONSHIP BETWEEN SLEEP HABITS AND OBESITY

The World Health Organization designated obesity as one of the most important public health threats because of the significant impact of chronic conditions associated with obesity, such as hypertension and type 2 diabetes. Although obesity is less prominently associated with morbidity in adolescence than adulthood (Berenson et al., 1998), a strong precursor of obesity and related morbidity in adulthood has been observed. In fact, the percentage of adolescents who

are overweight or obese has more than doubled since 1974 (Swinburn et al., 2011), and if these trends continue, it is estimated that by 2020 three of four Americans and seven of 10 people in the United Kingdom will be overweight or obese (Wang, McPherson, Marsh, Gortmaker, & Brown, 2011). Indeed several studies have shown that 50–80% of obese adolescents will become obese in adulthood (Guo & Chumlea, 1999; Must & Strauss, 1999).

Because of their public health importance, obesity in adolescence should be closely monitored. For adults, BMI values at or above 25 indicate overweight and a BMI at or above 30 defines obesity (Troiano & Flegal, 1998). In the 1990s, Must and Strauss defined adolescent obesity as a BMI in excess of the 75th percentile for at least 2 years between the ages of 13 and 17 years (Must & Strauss, 1999). However, 1 year later, Cole et al. developed internationally acceptable cutoff points for BMI for overweight and obesity by sex, between the ages of 2 and 18 years, defined as a BMI of 25 and 30 kg/m^2 at age 18, obtained by averaging data from 13 European countries as well as Israel and the United States (Cole, Bellizzi, Flegal, & Dietz, 2000).

Sleep deprivation in adolescence is a reality and has increased dramatically in the past half century. Throughout the literature there are numerous studies showing that poor or inadequate sleep duration increases the risk of various pathologies such as hypertension, cardiovascular disease, and most importantly, obesity (Shiromani, & Horvath, & Redline, & Van Cauter, & 2012). Indeed, a large study (n=9588) in which weight and sleep duration was measured during the years 1982–1984 and self-reported weights in 1987 and 1992 in the United States demonstrated that those who had less than 4 h of sleep a night were 73% more likely to be obese than those who had the recommended 7–9 h of rest (Gangwisch, Malaspina, Boden-Albala, & Heymsfield, 2005). Moreover, those who averaged 5 h of sleep had 50% greater risk, and those who had 6 h had 23% more (Figure 1) (Gangwisch et al., 2005).

Different causes could explain the relationship between reduced sleep duration and obesity in adolescence. A recent study demonstrated that in European adolescents (HELENA study), short sleep duration was associated with higher adiposity markers (Garaulet, Ortega, et al., 2011). The authors concluded that this association could be related to terms found in the energy balance equation: a combination of increased food intake and more sedentary habits (Garaulet, Ortega, et al., 2011). These data are consistent with those obtained by Van Cauter and Knutson, who postulated that both lower energy expenditure and excess of energy intake could be implicated in this interaction (Van Cauter & Knutson, 2008). On the one hand, epidemiological studies indicate that sleep deprivation may induce irregular eating habits such as increased snacking between meals, and could lead to obesity by increasing the time available to eat (Garaulet, Ortega, et al., 2011; Gluck, Venti, Salbe, Votruba, & Krakoff, 2011; Nishiura, Noguchi, & Hashimoto, 2010). One possible explanation resides in the fact that insufficient sleep increased the loss of lean body mass in obese adults (Nedeltcheva, Kilkus, Imperial, Schoeller, & Penev, 2010). Amino acids released from protein degradation may stimulate hypothalamic activity that increases appetite (Karnani et al., 2011). It is also known that inadequate sleep duration could produce alterations in leptin and/or ghrelin; both are involved in the mechanisms of hunger/satiety, thereby increasing the risk of overeating and, consequently, weight gain (Van Cauter & Knutson, 2008). On the other hand, it has also been suggested that sleep duration could lead to obesity by decreasing energy expenditure (increasing tiredness) as well as changes in thermoregulation (Garaulet, Ortega, et al., 2011; Gluck et al., 2011; Nishiura et al., 2010). Figure 2 summarizes the potential mechanisms by which sleep deprivation may predispose adolescents to obesity. These processes are detailed in the next sections.

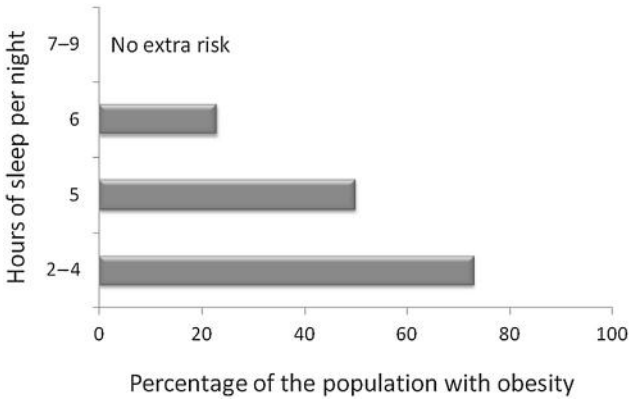

FIGURE 1 Short sleep raises the risk of obesity (Gangwisch et al., 2005).

ENERGY INTAKE, SLEEP, AND OBESITY

As mentioned earlier, the association between short sleep duration and obesity could be due to total energy intake. Indeed, a crossover inpatient study performed in 15 men and 15 women who were studied under short (4 h/night) and habitual (9 h/night) sleep conditions, in random order, for 5 nights showed that the reduction in sleep increased energy intake by 300 kcal (St-Onge et al., 2011). This study also showed that the effect was mostly due to increased consumption of fat, notably saturated fat, during short sleep, and this higher energy intake was not compensated by increased energy expenditure.

More specifically in adolescents, several epidemiological studies also reported associations between poor sleep duration and increased energy intake. Particularly, adolescents had an increased preference for high-caloric foods, most of which came from fat and fewer from carbohydrates (Beebe, Miller, Kirk, Daniels, & Amin, 2011; Nishiura et al., 2010; Weiss et al., 2010). Other studies confirmed associations

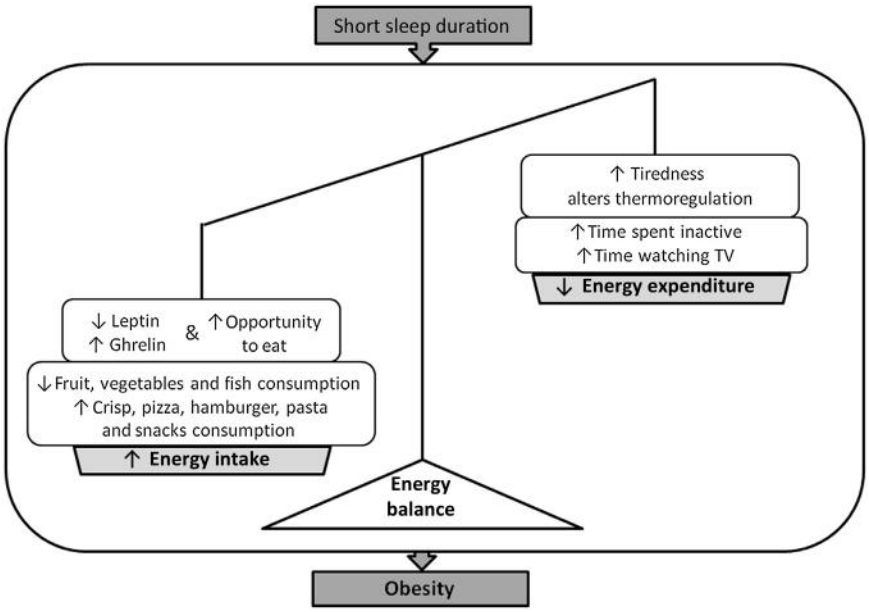

FIGURE 2 Potential mechanisms by which sleep deprivation may predispose to obesity. *Adapted from Garaulet, Ortega, et al. (2011).*

between short sleep and consumption of calorie-dense foods, but did not allow for an examination of macronutrient content. A recent study in European adolescents demonstrated that those considered to be shorter sleepers had a lower probability of having adequate food habits than those who slept more than 8 h per day (Garaulet, Ortega, et al., 2011). When the authors analyzed the results obtained from a food frequency questionnaire, they found that shorter sleepers did not consume an adequate amount of fruit, vegetables, and fish. Also, consumption of chips, pizza, hamburgers, pasta dishes, and snacks was higher compared with that of adolescents who slept more than 8 h per day. These data coincide with the observational study of Hitze et al., who found that short sleep was related to a lower nutritional score characterized by low consumption of healthy items (whole-grain products, milk products, fruit, vegetables and potatoes, and fish) and high consumption of risk-related items (white bread, meat products, soft drinks, fast food, and sweets) (Hitze et al., 2009). Similarly, other studies demonstrated that short sleep duration is associated with lower dietary quality in adolescents. For example European adolescents with insufficient and borderline insufficient sleep scored lower on the Diet Quality Index for Adolescents with Meal index (DQI-AM) than adolescents with optimal sleep duration (Bel et al., 2013). The DQI-AM was used to calculate overall dietary quality, considering the components' dietary equilibrium, dietary diversity, dietary quality, and a meal index. This supports the hypothesis that the health consequences of insufficient sleep may be mediated by the relationship of insufficient sleep to poor dietary quality.

Along the same lines, in a previous work Nedeltcheva et al. showed that bedtime curtailment was accompanied by an increased consumption of snacks (Nedeltcheva et al., 2010). Indeed, Weiss et al. observed that those short sleepers also consumed approximately 500 kcal from snacks more than those who slept more (Weiss et al., 2010). The causes of this association could be that: (1) short sleep duration produces an alteration in the levels of satiety hormones, i.e., decreased leptin and increased ghrelin, which can lead to an increase in hunger and appetite (Chaput, Despres, Bouchard, & Tremblay, 2007; Spiegel, Tasali, Penev, & Van Cauter, 2004); or (2) when we sleep less, we simply have more time and/or more opportunities to eat, and sleeping short hours in an obesity-promoting environment may facilitate the excessive consumption of energy from snacks but not meals (Figure 1).

Furthermore, sleep deprivation has been found to hinder attention and impulse control, thus leading to increased hedonistic eating. An interesting recent study showed that short sleep duration resulted in changes in neuronal activity when subjects were exposed to food stimuli, and the authors observed that brain regions associated with motivation and desire were affected (St-Onge et al., 2012). This fact could indicate an increased propensity for seeking food in individuals who have poor sleep duration.

These findings support the idea that short sleep duration or sleep deprivation is related to altered dietary quality, possibly leading to obesity (increasing BMI, waist and hip circumference, and body fat percentage) and other diet-associated health problems.

ENERGY EXPENDITURE, SLEEP, AND OBESITY

The other side of the equation of energy balance implicated in the association between short sleep and obesity is energy expenditure. Numerous studies demonstrated a direct

association between short sleep duration and decreased energy expenditure. Currently, adolescents frequently adopt habits that are not compatible with good sleep. Among inadequate sleep hygiene practices, some are more minutes watching television or using computers, especially in the period preceding bedtime, and more minutes spent inactive. These activities involve a decrease in energy expenditure by increasing fatigue, as well as changes in thermoregulation (Van Cauter & Knutson, 2008) (Figure 1). In this sense, a study by Garaulet et al. in which accelerometers (an objective method of choice to assess physical activity and sedentary time in a free-living environment (Westerterp, 2009)) were used showed that European adolescents who spent more time in sedentary behaviors was significantly higher among shorter sleepers than in those adolescents who slept at least 8 h per day (Garaulet, Ortega, et al., 2011). Indeed, in this study short sleepers reported more time watching television. These data coincide with several studies from the United Kingdom in which the authors showed that most television viewing carried out at or near bedtime reduced sleep time (Owens et al., 1999). Currently, it is a fact among adolescents that factors such as social opportunities, extracurricular activities, academic demands, and part-time jobs contribute to delayed bedtimes (Dahl & Lewin, 2002) and to an eveningness circadian preference (sleep and wake times delayed) (Dahl & Lewin, 2002). This was demonstrated in Belgium: Adolescents who watched more television, spent more time playing video games, and used the Internet went to bed later, spent less time in bed on weekdays, and reported higher levels of tiredness during the day (Van den Bulck, 2004).

Numerous studies show recommendations for increasing adolescents' sleep duration together with increasing physical activity and limiting television, video game, and computer use, particularly before bedtime (Moreno, Furtner, & Rivara, 2010). Recommendations are related to results showing that adolescents who engaged in more than 3.5 h of physical activity *per week* had more favorable measures of sleep quality, such as higher sleep efficiency and more slow-wave sleep than those who engaged in 3.5 h or less (Brand et al., 2010). In addition, other works demonstrated that average sleep duration among adolescents who participated in 15 or more minutes of vigorous physical activity five or more times per week was greater than for those who performed exercise only one time per week (Delisle, Werch, Wong, Bian, & Weiler, 2010). From these studies, it could be deduced that short sleep duration increases tiredness in adolescents and as a consequence they become more sedentary and adopt new habits that promote obesity.

CONCLUSION

The research reviewed here suggests that short sleep duration may increase the risk of obesity via several pathways related to a misbalance on both sides of the equation of energy balance: food intake and energy expenditure. Healthy habits in food intake and physical activity are recommended to improve sleep duration and quality. Furthermore, improving the correspondence between biological and social clocks will contribute to the management of obesity in adolescents.

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Chapter 10

Sleep and Hypoxemia in Adults

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The World Health Organization (WHO, 2000) estimates that obesity has reached epidemic proportions and is one of the greatest public health problems around the world. This disease is no longer a problem just for high-income countries, but it is also for ones in the developing world. Obesity is defined as abnormal or excessive fat accumulation that may be harmful to health. The WHO defines overweight as a body mass index (BMI) (weight in kilograms divided by the square of height in meters (kg/m^2)) ≥25 and obesity as a BMI ≥ 30. Voelker (2012) indicated that obesity rates in United States adults are projected to increase nationwide by 2030, exceeding 50% in 39 states and adding up to US $66 billion to the cost of treating obesity-related diseases; the author also stated that if current trends are not halted, the report indicated that by 2030 all 50 states could have adult obesity rates of at least 44%, 39 states would have rates of ≥50%, and in 13 states >60% of adults would be obese.

Increases in adult obesity would contribute to increases in new cases of type 2 diabetes, coronary heart disease and stroke, hypertension, arthritis, and cancer, according to the report. By 2030, treatment costs for preventable obesity-related diseases are expected to add between US $48 billion and US $66 billion to current costs that are estimated between US $147 billion and US $210 billion. Economic productivity losses are estimated to be between US $390 billion and US $580 billion by 2030.

It is well known that not only the amount of fat but also its distribution is associated with specific comorbidities affecting health differentially. Fat is an endocrine and paracrine tissue that secretes substances directly involved in affecting metabolism. Adipose tissue is not only a storage of fat, it is also the largest endocrine organ in the human body that secretes hormones, cytokines, and growth factors (Rajala & Scherer, 2003; Trayhurn & Wood, 2005).

Various comorbidities have been associated with obesity, such as cardiovascular, metabolic (in which fat distribution is important), psychiatric, psychological disturbances, and low quality of life. Sleep quality and quantity can be important mediators in how obesity contributes to various comorbidities.

Evidence shows that chronic reduction in total sleep time is associated with changes in the level of leptin and ghrelin, important hormones involved in the control of satiety and appetite. Leptin is a protein hormone produced mainly by fat cells. It regulates metabolic activity and has many other physiological functions. It is an anorexigenic hormone that inhibits feeding, increases sympathetic activation, modulates immune functions, influences synaptic activities, and often promotes inflammation. In sleep-deprived subjects leptin is decreased.

Ghrelin, another important hormone involved in feeding control, is a hunger-stimulating peptide mainly produced by the cell lining in the fundus of the human stomach and epsilon cells of the pancreas. Ghrelin levels rise before meals and during fasting, consistent with its proposed role in hunger and meal initiation. Ghrelin receptors are expressed in a wide variety of tissues, including the pituitary, stomach, intestine, pancreas, thymus, gonads, thyroid, and heart. In sleep-deprived subjects, ghrelin is increased. Therefore, a reduction in total sleep time can lead to an imbalance in the hormones that control appetite and lead to weight gain (Spiegel, Tasali, Penev, & Van Cauter, 2004).

In addition to hormonal changes associated with a reduction in the amount of sleep that could lead to increased body weight, obesity itself brings about changes in sleep, the best known of which is an increased risk of obstructive sleep apnea syndrome (OSAS), which in turn is associated with hypertension (Peppard, Young, Palta, & Skatrud, 2000; Shahar et al., 2001), diabetes (Shaw et al., 2008; Tasali,

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Mokhlesi, & Van Cauter, 2008), depression, daytime sleepiness (Roure et al., 2008), decreased daytime performance, and increase risk for occupational and vehicular accidents (Sassani et al., 2004).

OSAS is characterized by recurrent episodes of complete or partial upper airway collapse (episodes of apnea and hypopnea, respectively) accompanied by chronic IH and hypercapnia and fragmented sleep owing to cortical micro-arousals. The repetitive nature of the intermittent oxyhemoglobin desaturation that is classically observed in patients with OSAS and micro-arousals is associated with an acute increase in sympathetic nervous system activity leading to intermittent increases in blood pressure and heart rate and secondarily induced endothelial dysfunction, systemic inflammation, oxidative stress (Svatikova et al., 2005; Yamauchi et al., 2005), and metabolic abnormalities (Punjabi & Beamer, 2009).

Although both sleep fragmentation and IH are believed to contribute to the adverse effects of OSAS, their relative independent contribution and interaction is still poorly understood. Because IH and micro-arousals frequently occur simultaneously as the consequence of apnea or hypopnea, there is difficulty in differentiating these two downstream effects of obstructive respiratory events in clinical studies of OSAS. Many human studies use IH as the main factor in OSAS; therefore, this chapter will focus on IH.

The brain is sensitive to hypoxemia; therefore, it has been thought that the morbidity observed in OSAS is a result of chronic, cumulative effects of nocturnal IH. Among the physiological mechanisms that may be involved in the downstream deleterious effects of IH are elevation of sympathomimetic hormones (e.g., epinephrine and norepinephrine) as well as stress hormones (e.g., cortisol) (Narkiewicz & Somers, 2003) that could lead to an increase in hepatic gluconeogenesis and a decrease in skeletal muscle reuptake of glucose, resulting in insulin resistance and hyperglycemia. In addition, several distinct but synergistic pathways are involved, including an increase in oxidative stress (Svatikova et al., 2005; Yamauchi et al., 2005), dysregulation of the hypothalamic–pituitary–adrenal axis, and low-grade systemic inflammation (Sabato et al., 2006) with elevation of systemic inflammatory markers such as tumor necrosis factor-α, interleukin-6, and high-sensitivity C-reactive protein (Punjabi & Beamer, 2009).

In addition to these physiological changes, behavioral disturbances are present in OSAS, including cognitive, motor, autonomic, learning, and affective, and sleepiness and fatigue, which are observed in adult patients (Beebe, Groesz, Wells, Nichols, & McGee, 2003; Decary, Rouleau, & Montplaisir, 2000; Goncalves, Paiva, Ramos, & Guilleminault, 2004; Koseoglu et al., 2013). Furthermore, increased neurodegenerative changes and enhanced susceptibility to oxidative injury has been postulated as a likely consequence of IH associated with OSAS (Neubauer, 2001). A number of neuroimaging studies reported that adult patients who experience OSAS have regional gray and white matter loss and display alterations in markers of neuronal integrity and changes in prefrontal lobe perfusion (Alchanatis et al., 2004; Bartlett et al., 2004; Kamba et al., 2001; Macey et al., 2002). These neuroimaging studies suggest that the behavioral consequences of IH may be long-lasting or only partially reversible.

There are a large number of human studies of OSAS exploring the source of the neurocognitive complications, many of which are based on brain electrophysiologic and imaging studies. Electrophysiologic studies established a relationship between nerve conductance abnormalities and the severity of hypoxemia and partial recovery with treatment of OSAS. The event-related potentials (ERPs) technique has been used to explore the presence of cognitive dysfunction in OSAS. Subjects with severe OSAS (Respiratory Disturbance Index of 77.4 ± 27.5 and Oxygen Desaturation Index of 31.2 ± 31.0) showed longer visual P300 latencies (VL) (408.1 ± 34.9 ms vs control = 385.6 ± 31.6 ms) (Sangal & Sangal, 1997) that seemed visual specific, because auditory variables did not differ from that of controls. Despite significant improvement in sleep and respiratory variables and the level of objective daytime sleepiness (MSLT) after 2–4 months of continuous positive airway pressure (CPAP), there were no significant changes in P300 variables (amplitude and latency auditory and visual). The authors argued that prolonged VL in OSAS does not seem to be a simple result of sleepiness and may represent a distinct neurophysiological change, which suggests that the cognitive processing abnormality in OSAS is either irreversible or takes longer to improve than abnormalities in sleep and hypersomnia.

Inoue, Nanba, Kojima, Mitani, and Arai (2001) also showed abnormal P300 latency in patients with severe OSAS and found a difference in age to the response to CPAP treatment. Compared with controls, OSAS patients showed significantly longer latency of P300 that was not correlated with the level of sleepiness measured as mean MSLT, but the amount of hypoxemia (percent total sleep time with oxygen saturation <90%) correlated with P300 latency. During CPAP treatment, P300 latency was significantly shortened in the group of patients under 45 years of age, whereas older patients did not show a significant change. The authors speculated that P300 latencies might be prolonged owing to nocturnal hypoxemia and the abnormality might be irreversible, especially in older patients. Raggi and Ferri (2012) in a recent review of 23 empirical studies on ERPs in OSAS concluded that ERP studies demonstrated changes in cognitive attentive processing in

OSAS, mainly in association with altered functioning of the prefrontal cortex, and that CPAP treatment may improve vigilance, attention, and cerebral information processing in these patients. However, the remaining deficits during CPAP therapy may reflect irreversible hypoxic cerebral damage.

Neuroimaging techniques have also allowed the recognition of changes in brain structure, metabolism, activation, neural control, and brain impairment associated with respiratory abnormalities as OSAS. The application of magnetic resonance imaging (MRI) technology has allowed the identification of neural abnormalities associated with OSAS and also established the risk of poor outcome by determining the relationships between brain integrity and functional response to treatment. Positron emission tomography techniques have also led to improved understanding of disease characteristics and consequences (Ferini-Strambi, Marelli, Galbiati, & Castronovo, 2013; O'Donoghue et al., 2012; Weng et al., 2014; Yaouhi et al., 2009; Zimmerman & Aloia, 2006).

Structural imaging methods such as voxel-based morphometry (VBM) are automatic and quantitative methods for detecting group differences in gray matter (GM) concentration or volume, with improvement for spatial normalization and inter-subject registration. Weng et al. (2014) reported alterations in several GM regions, including areas that regulate memory, executive function, and affect (e.g., frontal cortex, anterior cingulate, and hippocampus).

Macey et al. (2002) compared GM in 21 men with OSAS and matched similar controls, and found significant reductions in GM in several brain regions (i.e., anterior cingulate, hippocampus, frontal, parietal, and temporal lobes) that correlated with OSAS severity. Interestingly, they found that total GM volume decreased with age in control subjects but not in subjects with OSAS, and the ratio of total gray to white matter was lower in subjects with OSAS. The authors stated that morphologic differences suggest two possibilities: (1) GM loss may be a consequence of OSAS, or (2) preexisting abnormalities may contribute to genesis or maintenance of the disorder. They speculated that at least a portion of the anatomic differences is likely to result from hypoxemic, hypercapnic, or reduced-perfusion consequences of OSAS.

Morrell et al. (2010) and Morrell et al. (2003) demonstrated that patients with OSAS had a significant reduction in GM volume in the right middle temporal gyrus, extending along the occipitotemporal sulcus inferiorly and left cerebellum compared with healthy controls. However, their data did not confirm previous reports of GM changes in the frontal and parietal cortices, anterior cingulate, or hippocampus (Macey et al., 2002; Yaouhi et al., 2009), areas that are important in autonomic regulation as well as cognitive function. In contrast, other investigators did not find significant structural changes. O'Donoghue et al. (2005) investigated volumetric changes using two different measurement methods in patients with severe OSAS with oxygen desaturation less than 90% for greater than 15% of total sleep time on the diagnostic polysomnogram. They included subjects without other comorbidities that might be associated with altered brain structure. Surprisingly, the authors found little indication of volume deficits in patients compared with controls. Using VBM, no areas of GM volume deficit or increase were found in patients with OSAS compared with controls when adjustment was made for multiple comparisons. Using region of interest (ROI) analysis, no differences were found in whole brain, temporal lobe, or hippocampal volumes. Treatment with CPAP over 6 months did not result in focal changes in GM concentration or in hippocampal or temporal lobe volume changes, although there was a small but significant decrease in whole brain volume.

Yaouhi et al. (2009) evaluated patients with OSAS ($n = 16$) with an extensive neuropsychological test battery to investigate attention and vigilance, executive functions, episodic memory, and motor domains. For brain imaging they used the optimized VBM procedure for the MRI data, resting-state ^{18}F-fluoro-2-deoxy-D-glucose positron emission tomography with correction for partial volume effects, and voxel-based analyses. In terms of neurobehavioral performance, patients displayed objective daytime somnolence but little impairment in memory and motor domains. Imaging data revealed GM loss in the frontal and temporo–parieto–occipital cortices, thalamus, and hippocampal region, and some basal ganglia and cerebellar regions, mainly in the right hemisphere. The decrease in brain metabolism was also right-lateralized but more restricted than the GM density changes, and involved the precuneus, the middle and posterior cingulate gyrus, and the parieto–occipital cortex, as well as the prefrontal cortex. They concluded that despite the presence of only minor memory and motor impairment, patients displayed significant cerebral changes in terms of both GM density and metabolic levels. They argued that patients may have benefited from cognitive reserve and compensatory mechanisms.

Canessa et al. (2011) studied 17 men with severe OSAS before and after CPAP treatment and found impairment in memory, attention, executive functions, and constructional abilities, as well as higher sleepiness and lower score on the Beck Depression Inventory in untreated patients with OSAS, and these impairments were associated with focal GM volume reductions in the left hippocampal entorhinal cortex, in the left posterior parietal cortex, and in the right superior frontal gyrus. After 3 months of treatment, a significant improvement in all cognitive domains was observed. This improvement was related to a GM volume increase in the hippocampus (left subiculum and bilateral

entorhinal cortex), the medial orbitofrontal cortex, and the rostral portion of the right superior frontal gyrus. When focusing on the cytoarchitectonic subdivision of the hippocampus, a GM volume increase was observed bilaterally in the cornu ammonis, entorhinal cortex, fascia dentata, and subiculum after treatment. These results were strengthened by the significant correlation between reduction of errors at the Stroop test and GM volume increase in the left subiculum in the VBM analysis, and in the cornu ammonis in the ROI analysis. In the case of the entorhinal cortex, the amount of GM increase after treatment was correlated with an improvement in verbal and visuospatial short-term memory, attention, and executive functioning, indicating a direct correlation between the GM changes and cognitive improvement. No significant increase in total intracranial volume was found and the average amount of GM volume increase was associated with a comparable yet nonstatistically significant reduction in cerebrospinal fluid volume. The authors proposed that regardless of the origin of the deficit, the mechanism of brain change could be vasogenic. They believed that the pattern of neuropsychologic changes in OSAS is similar to that seen in cases of mild cerebrovascular disease (most commonly small vessel disease).

From the review of these neuroimaging studies in OSAS, several important limitations and considerations have emerged. Apart from technological differences such as threshold settings, type of scanner, software, lack of appropriate statistical analysis with corrections for multiple comparisons, and so forth, there are those identified by Zimmerman and Aloia (2006): (1) Most studies included only male participants, thereby limiting generalizability; (2) few studies reported measures of intellectual or educational level that can potentially affect neuropsychological functions; (3) age may also modulate the effect of OSAS on brain structure and mask the effects of OSAS on brain integrity; (4) the length of undiagnosed illness is a potentially confounding variable that is difficult to assess in OSAS and not always examined (e.g., with questionnaires for bed partners of prior years of loud habitual snoring and witnessed apneas); (5) studies failed to adequately examine the effect of common comorbid medical conditions that may also be associated with alterations in brain structure and function (i.e., hypertension is commonly reported in patients with OSA and has known independent effects on brain structure and function).

Another important aspect indicated by Zimmerman and Aloia (2006) is the sampling bias that exists when conducting MRI scans on obese patients with OSAS. Although BMI is often reported in the reviewed studies, the effect of BMI on observed findings is generally not explored or discussed. In a practical sense, many patients with OSAS are unable to appropriately fit into an MRI scanner with a limit of 130 kg body weight. It is therefore likely that OSAS samples included in neuroimaging studies represent only a subgroup of patients with the disorder.

One of the most important considerations to be taken into account is the type of study design. Most studies had a cross-sectional design rather than a longitudinal one. Longitudinal studies may allow the researcher to more specifically establish the direction of causality by examining the development of underlying neuropathologic processes associated with OSAS comparing repeated scans over time in the same participant using the same MR scanner. Therefore, there is a need to further investigate the links between OSAS and brain structure and function in a longitudinal fashion.

There are not enough data regarding obesity as a risk factor for cognitive impairment. Recently, Elias, Elias, Sullivan, Wolf, and D'Agostino (2005) reported that obesity itself is an independent risk factor for cognitive decline that is gender dependent, because they found cognitive impairment in men but not in women (Elias et al., 2005). Also, there is not enough evidence regarding how much of the cognitive impairment seen in patients with obesity and OSAS is the result of OSAS and how much can be attributed to the effect of obesity independently of OSAS, because it is well known that there is a high prevalence of OSAS in this type of population (Valencia-Flores, Orea, et al., 2004; Valencia-Flores, Rebollar, et al., 2004). Therefore, it is necessary to have more research with respect to this.

Two of the most common comorbidities in obesity are diabetes type 2 and blood hypertension. In a recent work, Roberts et al. (2014) investigated the associations of diabetes and blood hypertension with image biomarkers of neuronal injury and ischemic damage to cognition in a population-based cohort without dementia. They found a different pattern of brain atrophy and cognitive impairment in diabetes and hypertension. Diabetes may affect late-life cognition through loss of brain volume, whereas hypertension may affect executive function through ischemic pathology. Our group of researchers also found different patterns of cognitive impairment associated with diabetes and hypertension in a sample of obese patients with OSAS who were studied with a validated and standardized test battery. We did not find significant differences in executive functions when the group of diabetic obese was compared with the non-diabetic–obese group, but we found significant impairment in executive functions associated with blood hypertension. Our investigation is in agreement with recent published data by Roberts et al. (2014) in a population-based cohort, and we extended these findings to an obese population (Rodríguez, 2013). Also to be considered when studies are performed in obese patients is the impact of depression on cognitive function. Depression has been associated with OSAS. In addition, the level of excessive daytime sleepiness must be considered. We previously reported that obese patients remain sleepy even when they had considerably reduced body weight and OSAS had been eliminated (Valencia-Flores, Orea, et al., 2004). Such results may reflect an

inflammatory process, as proposed by Vgontzas (2008), or permanent brain damage that needs to be ruled out.

OSAS has also been implicated in pathologic changes of the peripheral nervous system (Lüdemann, Dziewas, Sörös, Happe, & Frese, 2001; Mayer et al., 1998). More recently, Dziewas et al. (2006) tried to replicate previous findings from their group in which they reported an increased prevalence of axonal sensory polyneuropathy in patients with OSAS and a decreased sural sensory nerve action potential in OSAS compared with controls, and found a correlation of axonal dysfunction with oxygen desaturation. Those authors concluded that IH is an independent risk factor for axonal dysfunction of peripheral nerves and that there is a beneficial effect of treatment for OSAS on peripheral nerve function.

OSAS is a recognized risk factor for nonarteritic anterior ischemic optic neuropathy (Mojon et al., 2002; Palombi et al., 2006) and has been associated with a variety of ophthalmologic disorders (Waller, Bendel, & Kaplan, 2008) including glaucoma, floppy eyelid syndrome, and papilledema. Nocturnal hypoxemia of OSAS has been postulated to have a role in triggering these diseases. The recognition of these associations is important for primary care physicians, ophthalmologists, and sleep physicians.

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Chapter 11

Obesity Hypoventilation Syndrome

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INTRODUCTION

Obesity places a significant load on the respiratory system, altering chest wall mechanics, increasing the work of breathing (WOB), and promoting the development of upper airway obstruction during sleep. In extreme cases, abnormal breathing will also be present during wakefulness, manifested by daytime hypoventilation. When $PaCO_2$ is increased above 45 mm Hg during wakefulness in obese individuals (body mass index (BMI) > 30 kg/m^2), in the absence of other conditions that would better explain hypoventilation, a diagnosis of obesity hypoventilation syndrome (OHS) is made.

Distinguishing individuals with OHS from those with simple morbid obesity with or without obstructive sleep apnea (OSA) is not just an exercise in clinical curiosity. Endothelial dysfunction and systemic inflammation are significantly greater in people with OHS compared to eucapnic obese individuals (Borel et al., 2009), with higher risks of developing cardiovascular disease and lower likelihood of survival (Berg, Delaive, Manfreda, Walld, & Kryger, 2001; Borel et al., 2013; Jennum, Ibsen, & Kjellberg, 2013; Nowbar et al., 2004). There are also high health, personal, and societal costs associated with the development of OHS, occurring some years before a formal diagnosis is made (Berg et al., 2001; Jennum et al., 2013), and affecting not only the individual but also their partners (Jennum, Ibsen, & Kjellberg, 2014) (Figure 1). These findings highlight the importance of identifying patients with this disorder as early as possible. Once identified, effective intervention is crucial, and most commonly involves the use of positive airway pressure (PAP) therapy. Understanding why daytime hypercapnic respiratory failure develops in some obese individuals but not others is important not only in considering the choice of treatment but also in appreciating why PAP therapy may not be completely effective in reversing daytime hypercapnia.

MECHANISMS UNDERLYING THE DEVELOPMENT OF OHS

It would be easy to explain away the development of awake respiratory failure in OHS as simply a manifestation of extreme obesity and the mechanical restraints this places on the respiratory system. However, such arguments fail to explain why only a proportion of individuals even in the super-obesity categories (i.e., BMI > 50 kg/m^2) develop OHS while others remain normocapnic. Nevertheless, the prevalence of OHS does increase as BMI increases (Kaw, Hernandez, Walker, Aboussouan, & Mokhlesi, 2009). Data from animal and human studies have established that the development of awake hypercapnia in those with morbid obesity arises from a complex interaction of

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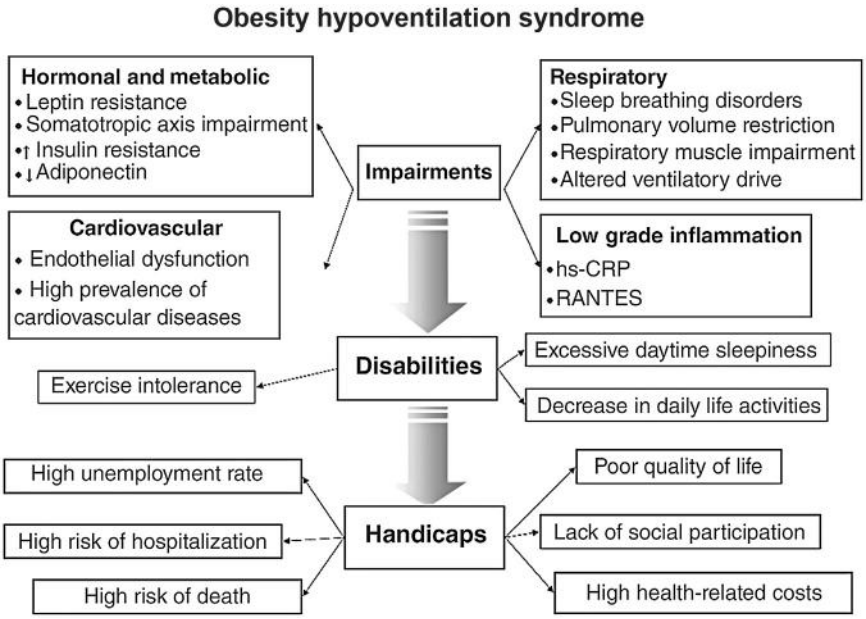

FIGURE 1 Illustration of the impairments associated with obesity hypoventilation syndrome (OHS), along with the disabilities and handicaps arising from this disorder. While OHS is thought of as a respiratory disorder, it is associated with significant cardiovascular and metabolic abnormalities. (Hs-CRP, high-sensitivity C-reactive protein; RANTES, regulated on activation, normal T-cell expressed and secreted.) *From Borel, Borel, et al. (2012), Respirology, with permission.*

circumstances including altered pulmonary mechanics, changes in respiratory drive, sleep-disordered breathing, and neurohormonal factors. While these circumstances are generally present in anyone with obesity, the development of awake hypoventilation occurs when the normal compensatory mechanisms designed to maintain ventilation in the face of the increased loads from obesity fail (Piper & Grunstein, 2010).

Obesity and Lung Function

Individuals with OHS exhibit a more central pattern of obesity, reflected in higher neck and waist:hip ratios (Resta et al., 2000). This excess adipose tissue around the thorax and abdomen restricts lung volumes, with vital capacity (VC), functional residual capacity (FRC), and expiratory reserve volume (ERV) all lower in OHS compared to eucapnic obese individuals. Breathing at low lung volumes has a number of physiological consequences, including reduced chest wall compliance and increased airway resistance, both of which will contribute to the markedly increased work of breathing seen in OHS compared to eucapnic obesity (Lee, Lin, Shen, Chiu, & Liaw, 2009). Low lung volumes also promote small airway closure and air trapping, imposing an additional load on breathing (Steier et al., 2009). Even when awake and sitting upright, OHS individuals have increased upper airway resistance (Lin, Wu, Chou, & Liaw, 2004), adding further to increased WOB. The increased mechanical loads on the respiratory system are substantially greater in those with OHS compared to eucapnic obese individuals even at similar levels of BMI (Lee et al., 2009; Lin et al., 2004).

At the same time, the capacity to meet this increased load is reduced. Although reports of respiratory muscle strength and endurance in obesity have varied, most reports have confirmed inspiratory muscle impairment in the presence of severe obesity or OHS (Collet et al., 2006; Rochester & Enson, 1974). In particular, impairment is likely to be present in OHS patients in the supine position, as this places the inspiratory muscles at a mechanical disadvantage either from the development of intrinsic positive end-expiratory pressure (PEEP) (Steier et al., 2009) or from overstretching of the diaphragm from the upward pressure of the abdominal mass (Sharp, Henry, Sweany, Meadows, & Pietras, 1964).

To reduce the high WOB, individuals with morbid obesity alter their respiratory pattern to one characterized by a higher breathing frequency and lower tidal volume (Chlif, Keochkerian, Choquet, Vaidie, & Ahmaidi, 2009), and this pattern is more marked in those with OHS (Pankow et al., 1997). Although this may assist in reducing the oxygen cost of breathing while maintaining high overall minute ventilation, such a pattern also increases dead space ventilation and eventually becomes disadvantageous as it worsens gas exchange, favoring a rise in CO_2. Small airway closure arising from reduced lung volumes also serves to worsen ventilation–perfusion matching, resulting in more pronounced hypoxemia in OHS compared to eucapnic obesity.

Respiratory Drive

Obese individuals have higher basal oxygen consumption and CO_2 production (Kress, Pohlman, Alverdy, & Hall, 1999) in addition to markedly increased WOB compared to normal-weight controls (Chlif et al., 2009; Sharp et al., 1964). In order to maintain eucapnia despite increased mechanical loads on the respiratory system,

resting ventilation must increase, and this is achieved by an increase in central respiratory drive (Chlif et al., 2009; Steier et al., 2009). Individuals with OHS, however, do not augment their drive to compensate for the increased load (Budweiser, Jorres, et al., 2007), and as a consequence minute ventilation is lower than required to maintain eucapnia. Ventilatory responsiveness to hypoxia and hypercapnia are also reduced in OHS compared to eucapnic individuals with or without obesity or OSA (Chouri-Pontarollo et al., 2007; Han et al., 2001), further promoting CO_2 retention. A more blunted ventilatory responsiveness to CO_2 is associated with more severe hypoventilation during rapid eye movement (REM) sleep (Chouri-Pontarollo et al., 2007). This reduction in chemoresponsiveness appears to be acquired, most likely from sleep-disordered breathing, since normalization of nocturnal breathing with PAP therapy produces improvements in ventilatory responsiveness to both carbon dioxide and oxygen even when BMI and lung function remain unchanged (Chouri-Pontarollo et al., 2007; Han et al., 2001; Redolfi et al., 2007).

Sleep-Disordered Breathing

Although sleep hypoventilation alone can be present in OHS (Kessler et al., 2001; Redolfi et al., 2007), around 90% of OHS patients also have upper airway obstruction (Olson & Zwillich, 2005), with no clinical or anthropometric differences between the two groups (Berger et al., 2001) (Figure 2). However, the development of awake hypercapnia in patients with OSA is the exception rather than the rule, and even among the morbidly obese sleep apneic only 25–30% will be hypercapnic (Macavei, Spurling, Loft, & Makker, 2013; Mokhlesi, Tulaimat, Faibussowitsch, Wang, & Evans, 2007). This suggests that other permissive factors must exist for the development of awake hypercapnia in obese individuals with OSA.

Differences in the pattern of ventilation between hypercapnic patients and those with eucapnia following obstructed nocturnal breathing have been observed, giving rise to a model that explains the process by which abnormal breathing during sleep eventually produces daytime hypercapnia (Berger, Goldring, & Rapoport, 2009). During apneic or hypopneic periods, a small accumulation of CO_2 occurs as ventilation is reduced or absent. Eucapnic individuals compensate for this by augmenting ventilation during the subsequent interapnea period, whereas hypercapnic patients demonstrate reduced ventilation for a given CO_2 load during this period (Berger et al., 2002). At the same time, the interapnea period is shorter in hypercapnic individuals, reducing the time available to unload CO_2 (Ayappa et al., 2002). These two features permit an acute rise in CO_2 overnight not seen in subjects able to maintain eucapnia (Chin et al., 1997). The overnight increase in CO_2 will be buffered by increased bicarbonate, but this in turn will blunt ventilatory responsiveness to CO_2 (Goldring, Turino, & Heinemann, 1971). Usually, these changes are very small over a single night, and both CO_2 and bicarbonate can be normalized during wakefulness over the next day. However, with further blunting of the ventilatory response to CO_2 or inadequate excretion of bicarbonate by the renal system, this balance will be upset, permitting daytime hypercapnia to emerge (Norman et al., 2006). Increased awake bicarbonate levels are a very sensitive, but not specific, predictor of OHS (Macavei et al., 2013; Mokhlesi et al., 2007), and correlate with more blunted CO_2 responsiveness (Raurich, Rialp, Ibanez, Llompart-Pou, & Ayestaran, 2010).

Subjects with OHS also experience more significant degrees of sleep hypoxemia than those with eucapnic OSA (Banerjee, Yee, Piper, Zwillich, & Grunstein, 2007; Kaw et al., 2009). Several studies have shown sleep time spent with $SpO_2 < 90\%$ is a strong predictor of daytime hypercapnia (Kaw et al., 2009; Resta et al., 2000). Sustained hypoxia could potentially interfere with neurotransmitters directly involved in respiratory control, or may delay arousal from sleep in the face of resistive loading (Hlavac et al., 2006), thereby extending periods of abnormal breathing permitting greater CO_2 retention during sleep.

Metabolic and Neurohormonal Influences on Ventilation

Overlaying this interplay between altered pulmonary function, reduced respiratory drive, and sleep-disordered breathing are the metabolic consequences of obesity, which could also influence breathing. Leptin, a protein designed to regulate appetite and energy expenditure, has been proposed as a potential contributor to the development and progression of hypoventilation. In humans, serum leptin levels are elevated in both obesity and OSA, and are suggested to be a compensatory mechanism to stimulate breathing in the presence of the increased ventilatory load created by obesity (Phipps, Starritt, Caterson, & Grunstein, 2002). Fasting serum leptin levels are higher in OHS patients compared to eucapnic obese individuals (Phipps et al., 2002). Hyperleptinemia has been shown to be associated with a reduction in both respiratory drive and ventilatory responsiveness to CO_2 in a group of very obese individuals (Campo et al., 2007), while in another study, hypercapnic ventilatory response was significantly lower in hypercapnic patients compared with those who were eucapnic despite similar levels of serum leptin (Makinodan et al., 2008). These data suggest that leptin acts to augment respiratory drive in obese individuals in order to maintain eucapnia. However, some individuals develop a "resistance" to the stimulatory effects of leptin on ventilation, so that despite high serum levels of leptin they will continue to hypoventilate. Leptin may also be

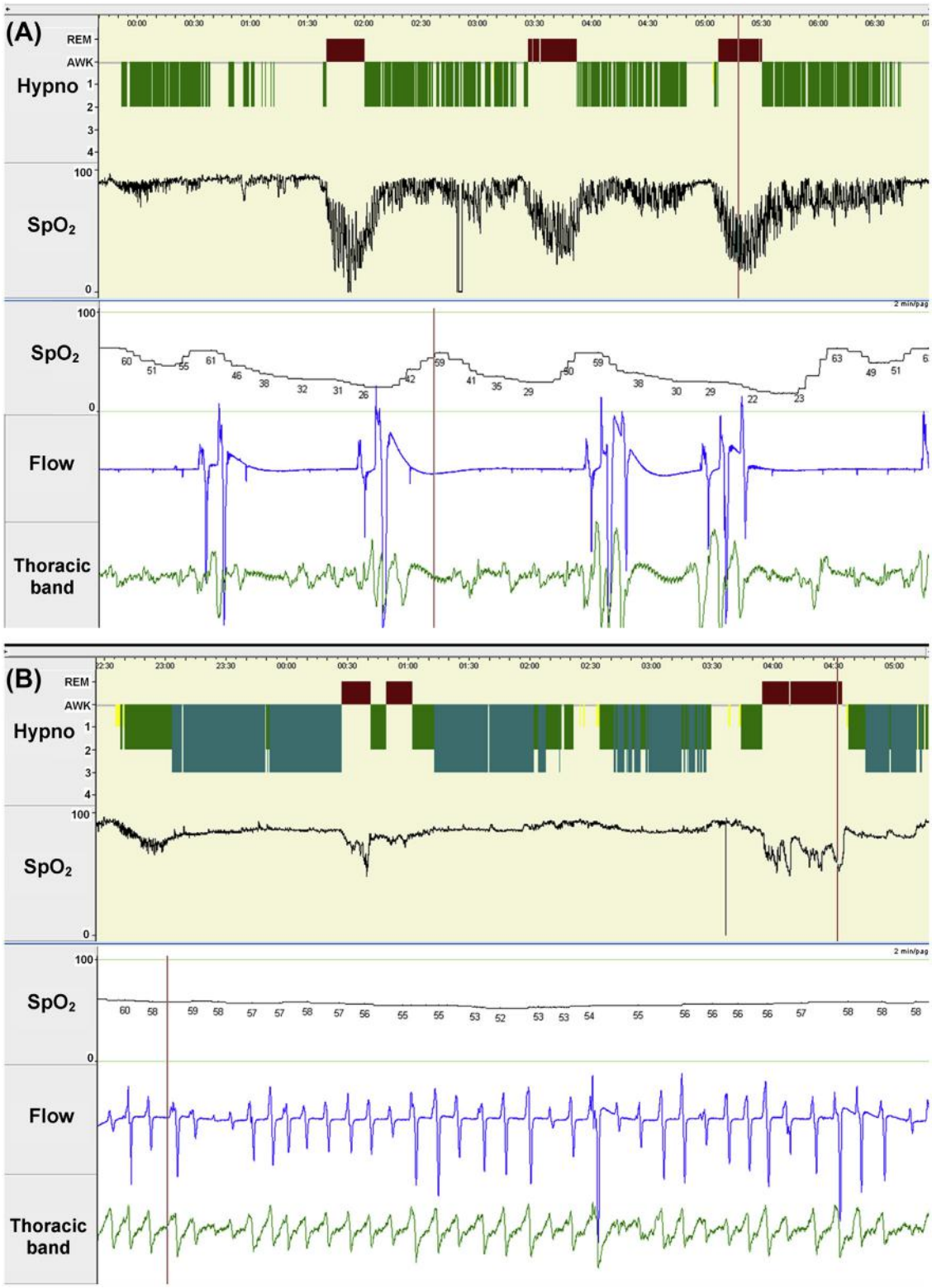

FIGURE 2 Patterns of sleep-disordered breathing in obesity hypoventilation syndrome (OHS). (A) The first two channels depict the overnight sleep stages (Hypno) and oxygen saturation (SpO_2) in a patient with repetitive obstructive events throughout sleep. During rapid eye movement (REM) sleep, these obstructive events are superimposed on hypoventilation, resulting in profound desaturation. The three lower channels illustrate the breathing pattern during a 2-min epoch of REM sleep. Despite continued respiratory efforts (thoracic band), there is no airflow (Flow), signifying obstructive events. Despite several recovery breaths between events, SpO_2 fails to return to baseline levels during this period. Obstructive apnea is present in the majority of patients with OHS. (B) In this patient, the most obvious periods of abnormality are confined to REM sleep only. The lower three channels demonstrate nonapneic breathing but a sustained low saturation, typical of sleep hypoventilation. This type of sleep-disordered breathing is seen in around 10% of individuals with OHS.

involved in maintaining neuromuscular control of the upper airway muscles during sleep through increased respiratory drive (Polotsky et al., 2012). Resistance to leptin could reduce this drive, promoting pharyngeal collapse, and contributing to the high incidence of apnea and hypopnea seen in patients with OHS.

In OHS, the hormone insulin-like growth factor-1 (IGF-1) is significantly lower compared to obese controls, and inversely associated with $PaCO_2$ and positively associated with VC, two significant features of OHS (Monneret et al., 2010). IGF-1 has also been associated with ventilatory responsiveness to CO_2 in other disorders (Lindgren, Hellstrom, Ritzen, & Milerad, 1999). This highlights the potential for various metabolic and hormonal factors to promote or modify compensatory mechanisms designed to maintain eucapnia in the presence of excessive weight.

CLINICAL CONSEQUENCES OF OHS

Patients with OHS demonstrate significant cardiovascular morbidity, with higher prevalence rates of hypertension, congestive heart failure, pulmonary hypertension, and cor pulmonale than weight-matched eucapnic individuals (Berg et al., 2001; Borel et al., 2009; Kessler et al., 2001). The excess cardiovascular burden seen in OHS is not particularly surprising given the clinical characteristics of these individuals: markedly increased mechanical load on the respiratory system resulting in a high WOB (Lee et al., 2009); high circulating leptin levels (Phipps et al., 2002); a significant hypoxic burden (Kaw et al., 2009); and moderate to severe OSA (Kaw et al., 2009; Kessler et al., 2001). All these factors are associated with systemic inflammation and increased cytokine production, and are more markedly abnormal in patients with OHS (Borel et al., 2009). This, along with more severe endothelial dysfunction (Borel et al., 2009) and higher triglyceride levels (Monneret et al., 2010) compared to eucapnic obesity, places the OHS patient at significant risk of developing cardiovascular comorbidities.

These morbidities are present several years prior to a diagnosis of OHS being made (Jennum et al., 2013), and despite frequent contact with the health care system, the presence of hypoventilation and its consequences are often overlooked (Berg et al., 2001; Marik & Desai, 2013). At least one-third of patients with OHS are likely to present with acute hypercapnic respiratory failure (Borel et al., 2013; Priou et al., 2010), and even then the diagnosis may not be made or the institution of appropriate therapy undertaken (Marik & Desai, 2013; Nowbar et al., 2004). A late diagnosis can result in the development of significant secondary consequences, with poorer clinical outcomes even when intervention is commenced (Borel et al., 2013; Marik & Desai, 2013).

TREATMENT MODALITIES AND OUTCOMES

Pharmacotherapy

Improvements in ventilatory responsiveness to CO_2, resting ventilation, and daytime blood gases have been reported following the use of respiratory stimulant medications including medroxyprogesterone (Sutton, Zwillich, Creagh, Pierson, & Weil, 1975) and acetazolamide (Raurich et al., 2010). However, these have been short-term observational studies, and there is a paucity of data regarding the safety and longer-term benefits of using medication to improve respiratory drive. Currently, pharmacotherapy is not recommended as the primary therapy in OHS (Chau, Lam, Wong, Mokhlesi, & Chung, 2012).

PAP Therapy

PAP to manage sleep-disordered breathing can be delivered either as continuous (CPAP) or bilevel (BPAP) therapy. With CPAP therapy, a single level of pressure is delivered throughout the respiratory cycle, splinting the upper airway open. In addition, FRC is increased, which assists in reducing the WOB by offsetting intrinsic PEEP (Steier et al., 2009) while improving hypoxemia through prevention of small airway closure and better ventilation–perfusion matching. BPAP delivers two levels of pressure: a higher pressure during inspiration (IPAP), with the aim of increasing tidal volumes while reducing inspiratory effort; and a lower pressure during expiration (EPAP), which provides the same benefits as CPAP. Furthermore, the trigger to inspiratory support may be entirely patient-generated, known as spontaneous (S) mode; entirely machine-generated, known as timed (T) mode; or a combination of the two, referred to as spontaneous-time (ST) mode. Volume-targeted pressure support is a more recent approach to home ventilation whereby the device is set to automatically adjust the level of pressure support delivered in order to provide a guaranteed preset tidal volume or minute ventilation, usually in the range of 8–10 mL/kg ideal body weight for OHS (Berry et al., 2010; Murphy et al., 2012; Storre et al., 2006).

Continuous Positive Airway Pressure

Since obstructive events are common in the majority of patients with OHS, titration of PAP usually starts with CPAP, with the aim of eliminating obstruction and increasing nocturnal $SpO_2 > 90\%$. If sleep hypoxemia or hypopneas persist, or if nocturnal CO_2 remains high, the patient is switched to BPAP. With this approach around 50–80% of stable OHS patients presenting to a sleep laboratory can be managed with CPAP therapy (Banerjee et al., 2007; Mokhlesi et al., 2006). In many centers, the

decision that CPAP has "failed" is based on the initial titration night. However, several studies have demonstrated a progressive improvement in nocturnal gas exchange following the commencement of CPAP can occur (Piper, Wang, Yee, Barnes, & Grunstein, 2008; Salord et al., 2013). In a randomized study comparing CPAP to BPAP, no between-group differences in improvement in daytime arterial blood gases, resolution of daytime sleepiness, or therapy compliance therapy were found (Piper et al., 2008). In those allocated to CPAP, the median sleep time spent with $SpO_2 < 90\%$ during the initial CPAP titration was 39% (range, 16–80%). However, at the completion of the 3-month study, only 4 of the 18 patients continued to show nocturnal hypoxemia despite optimal CPAP pressures and were transferred to BPAP (Piper et al., 2008). While there is no definitive means of identifying CPAP responders and nonresponders prior to a titration study, more sleep time on CPAP spent with $SpO_2 < 90\%$, more restrictive pulmonary abnormalities reflected in lower VC, and higher $PaCO_2$ after one month of therapy are all associated with longer-term CPAP failure (Banerjee et al., 2007; Salord et al., 2013). Consequently, a reasonable clinical approach in OHS patients with concurrent upper airway obstruction is to optimally titrate CPAP first. Where sleep hypoxemia persists, follow up nocturnal oximtery and awake $PaCO_2$ should be performed within a month or so to detect any ongoing treatment failure, with a transfer to BPAP therapy if nocturnal hypoxemia or daytime hypercapnia persists (Salord et al., 2013).

Autotitrating CPAP machines are widely available that are capable of automatically adjusting the pressure in response to obstructed breathing. However, the algorithms used by these devices have not been tested in OHS and therefore cannot be recommended at this time. In patients presenting with sleep hypoventilation alone (i.e., AHI < 5/h) or with acute respiratory decompensation, BPAP is generally used as initial therapy.

BPAP Therapy

In many regions, OHS has become the most common indication for home ventilation (Garner et al., 2013; Lloyd-Owen et al., 2005). Despite this, no medium- or long-term studies have directly evaluated the various modes of BPAP and their impact on clinical outcome. In a study of 10 OHS patients already established on BPAP-ST, changing from an ST mode with a low (around 11 breaths/min) or high (around 21 breaths/min) backup rate to an S mode resulted in a high number of abnormal respiratory events (mainly central) and oxygen desaturation, leading the authors to query whether BPAP-S should be used for OHS (Contal et al., 2013). However, no other ventilator settings were adjusted prior to the study apart from the backup rate, and the data suggested significant upper airway obstruction persisted with both the S and low-rate ST modes. Arousals from these obstructive events could have produced variations in tidal volume, and as a consequence of rapidly changing CO_2 created central events. The findings are a reminder of the importance of titrating BPAP settings optimally for the mode used.

The majority of studies evaluating modes have compared BPAP-ST with a fixed pressure support to BPAP-ST with volume-targeted pressure support (Janssens, Metzger, & Sforza, 2009; Murphy et al., 2012; Storre et al., 2006). In the largest of these randomized studies, no between-group differences in change in $PaCO_2$, anthropometric measures, or health-related quality-of-life over a 3-month period were seen. Of interest, irrespective of whether pressure support was fixed or variable, those patients where more of the breaths were machine triggered (i.e., more passive ventilation) experienced better control of nocturnal CO_2, lower daytime CO_2 levels, and enhanced quality-of-life at 3 months (Murphy et al., 2012).

The existing data suggests both CPAP and BPAP can significantly improve nocturnal gas exchange, reverse diurnal hypoventilation, and improve quality of life (Mokhlesi et al., 2006; Murphy et al., 2012; Perez de Llano et al., 2005; Piper et al., 2008; Storre et al., 2006). However, a major limitation in assessing clinical outcomes of patients managed with CPAP is the lack of long-term data available for this group. Consequently, it is unclear whether patients with OHS managed with CPAP either from the outset of their diagnosis or after a short period on BPAP do as well or worse in the longer term than BPAP-treated individuals. Since there can be substantial cost difference between CPAP and BPAP, especially with the more complex modes, and significant health and social costs of poorly managed disease (Berg et al., 2001; Jennum et al., 2013; Jennum & Kjellberg, 2011), further evaluation of the various PAP modes is crucial in order to make the best clinical decisions around care for these individuals.

Outcomes of PAP Therapy

Reversal of some factors contributing to hypoventilation occurs with the use of CPAP and BPAP, even in the absence of significant weight loss. Respiratory drive and ventilatory responsiveness to CO_2 significantly improve, but are rarely normalized (Budweiser, Jorres, et al., 2007; Chouri-Pontarollo et al., 2007; Han et al., 2001). Reduced bicarbonate and improved sleep quality may account for these changes (Borel, Tamisier, et al., 2012). Lung volumes increase and take around 12 months to plateau (Heinemann, Budweiser, Dobroschke, & Pfeifer, 2007). Functional capacity also improves, with reduced time spent immobile (Murphy et al., 2012) and increased 6-min walk distances reported (Castro-Anon et al., 2012). Although BPAP has been shown to improve pulmonary hemodynamics in

OHS (Castro-Anon et al., 2012), mild to moderate pulmonary hypertension persists in some individuals despite correction of nocturnal gas exchange and is associated with poorer quality-of-life, especially in domains related to physical functioning and subjective exercise capacity (Kauppert et al., 2013).

Adherence to therapy is a critical factor in achieving long-term benefits with PAP therapy, and at least 4–4.5 h nightly use is required before consistent improvements in awake $PaCO_2$ and PaO_2 are seen (Mokhlesi et al., 2006; Murphy et al., 2012). However, despite good usage, up to 25% of OHS patients may continue to demonstrate some degree of daytime hypercapnia (Mokhlesi et al., 2006). In some, this may reflect significant abnormalities in patient–ventilator interactions, including leak, residual upper airway obstruction, or desynchronization, which can affect sleep quality and gas exchange (Contal et al., 2013; Fanfulla et al., 2007; Guo, Sforza, & Janssens, 2007). Mokhlesi et al. (2006) suggested that persisting hypercapnia may reflect obesity itself as the major contributor to the development of hypoventilation in these individuals, so that reversal of sleep-disordered breathing and improved respiratory drive can only partially correct the problem. Achieving and maintaining weight loss would be key to achieving daytime normocapnia in this group.

The full clinical implications of incomplete normalization of CO_2 despite good control of nocturnal breathing and gas exchange are unclear, and there are no studies comparing long-term outcomes between OHS patients achieving normocapnia and those who remain mildly hypercapnic. A retrospective study of OHS managed with BPAP for up to 10 years found that a reduction in $PaCO_2 > 23\%$ and a fall in hemoglobin compared to baseline were both associated with better prognosis (Budweiser, Riedl, Jorres, Heinemann, & Pfeifer, 2007). Whether there is a threshold value for awake CO_2 below which better clinical outcomes are achieved is not known. However, the requirement for ongoing oxygen therapy is an independent predictor of higher mortality (Priou et al., 2010), and should flag the individual in whom more careful monitoring and follow-up is required.

Weight Loss and Lifestyle Modifications

Weight loss can ameliorate many of the breathing abnormalities associated with OHS by addressing all three major mechanisms contributing to the disorder: improving pulmonary function (Sugerman et al., 1992), reducing the severity of upper airway obstruction (Dixon et al., 2012), and increasing respiratory drive (Rochester & Enson, 1974). Although weight loss may be achieved through diet and lifestyle modification, bariatric surgery generally provides a more rapid and long-term solution. Nevertheless, OSA may only be partially corrected even with significant weight loss (Dixon et al., 2012), and consequently patients should be reviewed to determine if and when PAP therapy for sleep-disordered breathing can be removed.

Weight loss also addresses the metabolic and inflammatory aspects of obesity. Although BPAP improves survival compared to no treatment (Pepin, Borel, & Janssens, 2012; Perez de Llano et al., 2005), cardiovascular morbidity related to extreme obesity persists. There is currently no evidence that BPAP significantly alters inflammatory, metabolic, or cardiovascular markers despite significant improvements in sleep architecture and gas exchange (Borel, Tamisier, et al., 2012). Furthermore, the persistence of high inflammatory markers (Budweiser, Riedl, et al., 2007) or cardiovascular abnormalities (Borel et al., 2013) despite noninvasive ventilation has been associated with a higher risk of death. Weight loss should be advocated for all individuals with OHS as part of a holistic approach to managing the respiratory and cardiovascular consequences of this disorder (Borel, Borel, et al., 2012).

Although BPAP may improve physical activity levels and promotes weight loss to some degree (Murphy et al., 2012), these changes are small and more formal exercise and activity programs need to be implemented. Increased physical activity is needed not only for weight maintenance but also to improve metabolic profile, reduce visceral fat accumulation, and diminish cardiovascular risk (Borel, Tamisier, et al., 2012). Dyspnea can pose a significant deterrent to exercise, and adjunctive techniques such as BPAP-assisted exercise training (Dreher, Kabitz, Burgardt, Walterspacher, & Windisch, 2010) and inspiratory muscle-strengthening programs (Villiot-Danger et al., 2011) may need to be implemented. In addition, motivation, and pain and exercise fear avoidance beliefs, may be significant barriers to participation in formal exercise programs and reinforce sedentary behaviors (Jordan, Ali, & Shneerson, 2009; Wingo et al., 2013).

CONCLUSION

OHS is a serious medical disorder, which is frequently overlooked in the differential diagnoses of patients presenting to hospital with respiratory, metabolic, and cardiovascular complaints. Once identified, the condition is most commonly treated using positive pressure therapy to manage sleep-disordered breathing. However, this approach only addresses one aspect of the disorder, and while it is usually effective in reversing daytime respiratory failure and improving respiratory drive, the inflammatory and microvascular abnormalities associated with the obesity aspects of the disorder remain. There is a growing awareness of the need to provide a more multifaceted management approach for these individuals, including weight loss and lifestyle modification, to reduce the ongoing cardiovascular risk they face even when sleep-disordered breathing has been well controlled.

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Chapter 12

Sleep, Sexual Function, and Testosterone

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Sleep plays an important, but often underestimated, role in sexual function throughout life. Beginning with puberty, normal sleep is required for development of the pituitary–gonadal axis. The effect of sleep on sexual function after puberty can be explained partly by the effects of sleep disruption on hormonal abnormalities, especially testosterone regulation. This chapter will explore how sleep and sleep disruption affect sexual function; first, determinants of sexual function and methodology for its assessment are briefly discussed.

PITUITARY–GONADAL AXIS

It is important to understand the normal male pituitary–gonadal axis in order to understand the interactions between sexual function, sleep, and testosterone.

In adult males, hypothalamic gonadotropin-releasing hormone (GnRH) is released in a pulsatile fashion with a pulse frequency of approximately one every 2 h. This travels to the pituitary gland via a short portal venous system. GnRH signals the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the anterior pituitary (see Figure 1). The release of LH and FSH are dependent on this pulsatile release of GnRH as constant exposure to GnRH results in paradoxical suppression of LH and FSH. In addition to this pulsatile release, GnRH fluctuates in both diurnal and seasonal rhythms.

LH and FSH act at the level of the testes. Within the testes, LH primarily acts on the Leydig cells to stimulate testosterone synthesis and FSH acts on the Sertoli cells to regulate spermatogenesis. In men, the testes produce 95% of testosterone (Bhasin, 2012).

There are multiple regulatory feedback systems in the male pituitary–gonadal axis that act primarily at the level of the hypothalamus, but can also affect the pituitary. Of importance to this discussion, androgens and estrogens both have an inhibitory effect on this axis. There are estrogen and androgen receptors in both the hypothalamus and anterior pituitary.

Testosterone acts in two ways. First, testosterone acts at the level of the hypothalamus, directly decreasing release of GnRH. Second, testosterone acts directly on the anterior pituitary to decrease the response of LH secretory cells to GnRH. Estradiol also negatively feeds back on gonadotropin release. This feedback is primarily at the level of the hypothalamus.

Hormonal measures in obese men are characterized by elevations in estrogen and decreased levels of FSH, LH, free testosterone, and total testosterone (Schneider, Kirschner, Berkowitz, & Ertel, 1979; Zumoff et al., 1990). These abnormalities become greater as the degree of obesity increases. One physiologic explanation for this finding is an increase in peripheral conversion of androgens to estrogens by aromatase (see Figure 1) in adipose tissue. This aromatase enzyme complex, aromatase cytochrome P450, is found in adipose tissue as well as liver, skin, and testicular Leydig cells. Zumoff, Miller, and Strain (2003) further

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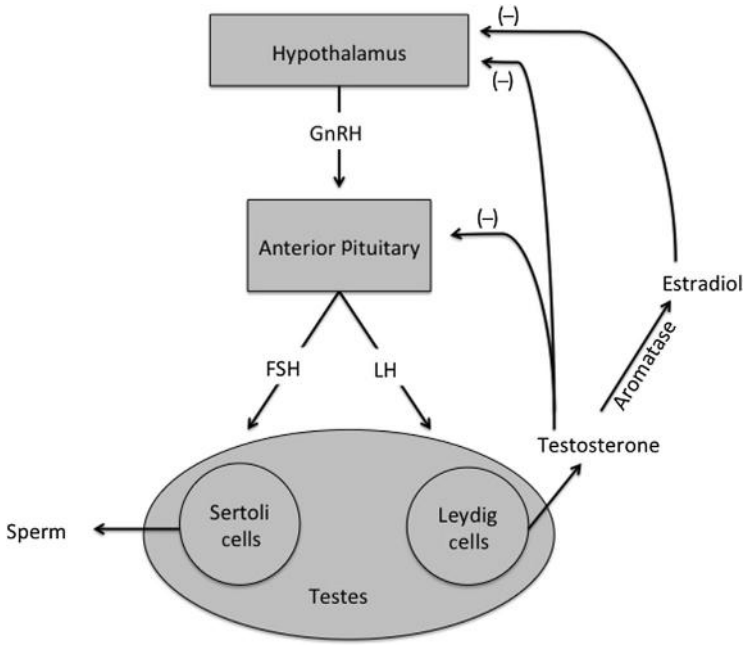

FIGURE 1 The hypothalamic-pituitary–gonadal axis and feedback. GnRH, gonadotropin-releasing hormone; FSH, follicle-stimulating hormone; LH, luteinizing hormone.

evaluated this mechanism by administering an aromatase inhibitor to obese men. Inhibition of aromatase resulted in a significant 24-h mean decrease in estradiol with an increase in testosterone and LH. These findings support the role of aromatase in the production of estradiol in obesity and the negative effect of estradiol on LH and, subsequently, testosterone production.

PITUITARY–GONADAL AXIS DURING SLEEP IN HEALTHY MALES

A diurnal variation in testosterone has been well documented in young, healthy males. Testosterone levels reach a peak in the morning. However, this diurnal variation decreases with increasing age (Plymate, Tenover, & Bremner, 1989).

The diurnal rhythm of testosterone is due to both the circadian and sleep-dependent rhythm of LH secretion. Since the 1970s, it has been understood that LH secretion increases at night in pubertal males. With the onset of male puberty, there is a marked rise in GnRH and, subsequently, LH. This secretion of LH is greatest during sleep. The relationship between LH and sleep in pubertal males remains under conditions of sleep–wake reversal (Kapen, Boyar, Finkelstein, Hellman, & Weitzman, 1974). During sleep, the LH pulses are related to slow-wave sleep (Shaw et al., 2012). These findings suggest that sleep during puberty plays an important role in reproductive development.

The diurnal variation in testosterone levels has also been directly linked to sleep in adult males. Luboshitzky, Herer, Levi, Shen-Orr, and Lavie (1999) evaluated the relationship between rapid eye movement (REM) sleep and testosterone secretion in young, healthy males. All subjects had normal secondary sexual characteristics and normal baseline hormonal values and were not taking any medications. Blood samples were collected every 15 min from 1900 to 0700 h. Electrodes were attached for monitoring of sleep stage and lights were turned off at 2200 h. Blood samples were evaluated for LH, FSH, and total testosterone. They found that testosterone begins to rise shortly after falling asleep, peaks at the first REM and stays elevated until awakening. The slope of the testosterone increase from sleep to the first REM significantly correlated with REM latency ($p < 0.05$). These findings suggest that REM sleep affects this nocturnal rise in testosterone.

Pulsatile LH secretion at night becomes less pronounced with age. Tenover, Matsumoto, Clifton, and Bremner (1988) found a slowing of LH pulse frequency during the night in young, healthy males (average age 30.4 years) with a trend toward increased amplitude of these pulses. This circadian rhythm was not found in a comparison group of older men (average age 70.4 years).

SEXUAL DYSFUNCTION

Males

Male sexual function is assessed by evaluation of erectile function, libido, and ejaculatory function. The prevalence of erectile dysfunction (ED) in the US adult male population over 20 years of age was 18.4% in a cross-sectional analysis of National Health and Nutrition Examination Survey (NHANES) data (Selvin, Burnett, & Platz, 2007). This estimates that ED currently affects 18 million men. The prevalence of ED increases with age. The prevalence of ED in

men younger than 40 years of age is 1–10% and increases to 20–40% in men 60–69 years of age (Lewis et al., 2010). Therefore, this is a growing medical problem in our aging population.

Assessment of sexual dysfunction includes a history and physical as well as assessment for hypogonadism. Clinical findings in hypogonadism are often nonspecific, including decreased libido, low energy, reduced muscle strength, and many others. Therefore, it is important to further evaluate with laboratory measurements. Given the diurnal fluctuations in testosterone, laboratory evaluation of hypogonadism should start with measurement of morning total testosterone level (Bhasin et al., 2010). Diagnosis should then be confirmed with a repeat morning total testosterone level. Testosterone primarily exists bound to either albumin or sex-hormone binding globulin (SHBG). Only approximately 0.5–3% of circulating testosterone exists as free hormone (Bhasin, 2012). However, because testosterone is weakly bound to albumin, this portion of testosterone is often referred to as "bioavailable." Therefore, total testosterone includes free testosterone as well as that bound to SHBG and albumin. Per recommendations from the Endocrine Society Guidelines (Bhasin et al., 2010), free testosterone should be measured only if there is suspicion for low levels of SHBG and the total testosterone measurement is at the lower limits of normal. However, of particular importance to this discussion, low levels of SHBG are found in both obesity and obstructive sleep apnea (OSA) (Grunstein et al., 1989).

Hypogonadism can occur as a result of testicular failure (primary) or problems at the level of the pituitary and hypothalamus (secondary). These two etiologies can be differentiated by measurement of LH and FSH. Primary hypogonadism will have elevated LH and FSH while secondary hypogonadism will present with low or inappropriately normal LH and FSH. Sleep-related hypogonadism is thought to be secondary.

Erectile Dysfunction: Pathophysiology and Risk Factors

The ability to have and maintain an erection is a vascular event. However, this requires the input and coordination of the neurologic, endocrine, and psychological systems.

Erectile function requires proper functioning of the vascular system. Therefore, it is not surprising that cardiovascular disease is a major risk factor for ED. Atherosclerosis, hypertension, diabetes mellitus, hyperlipidemia, obesity, and cigarette smoking have all been linked to ED (Jackson, 2007).

Medication side effects can also cause ED. It is important to remember the role of medication-induced ED as this can be a reversible cause. Antihypertensives, antidepressants, and antipsychotics are some of the most-recognized drugs that can interfere with erectile function. In a review of 120 patients presenting to an outpatient clinic with ED, a medication was implicated as the cause in 25% of patients (Slag et al., 1983).

There is increasing evidence that obesity is an independent risk factor for ED. Among men presenting to clinic for evaluation of ED, 79% were reported as overweight (Walczak, Lokhandwala, Hodge, & Guay, 2002). In one of the largest U.S studies of ED with evaluation of 31,742 men, obesity was associated with a higher risk of ED (relative risk, 1.3 (CI, 1.2–1.4)) (Bacon et al., 2003).

ED has been shown to improve with weight loss. Hammoud et al. (2009) evaluated sexual quality of life among obese men at baseline and after gastric bypass surgery. They evaluated sexual quality of life with the impact of weight on quality of life. This questionnaire, in addition to other parameters, evaluates lack of enjoyment of sexual activity, lack of sexual desire, difficulty with sexual performance and avoidance of sexual encounters. Increased weight significantly correlated with the total score of sexual dissatisfaction. Specifically, increased weight was associated with increased avoidance of sexual encounters and difficulty with sexual performance. Patients who underwent Roux-en-y gastric bypass and controls were followed for 2 years. BMI decreased by $16.6 \pm 1.2\,kg/m^2$ in the gastric bypass group while the control group had no significant change in weight. The weight loss group experienced an improvement in all sexual quality of life measurements while the control group did not change. These results support the independent negative effect of obesity on sexual quality of life.

Weight loss through increased physical activity has also been associated with improvements in sexual function. In a randomized trial of 55 obese males with ED, half of the subjects were provided specific advice on weight loss and exercise. After 2 years, the intervention group had a significant decrease in BMI and increase in physical activity. This group had a significant improvement in erectile function score, with 31% of them regaining sexual function (Esposito et al., 2004).

Low testosterone levels in men have been associated with ED and decreased libido (Cunningham, Hirshkowitz, Korenman, & Karacan, 1990). Animal models suggest that testosterone is related to ED by causing veno-occlusive dysfunction in the corpus cavernosum of the penis (Traish, Munarriz, O'Connell, & Choi, 2003). Supplementation of testosterone in men with hypogonadism results in increases in libido and sleep-related erections (Cunningham et al., 1990; Snyder et al., 2000). A randomized controlled trial evaluating the effects of testosterone supplementation on sexual quality of life found a significant increase in sexual desire, nighttime erections, and intercourse frequency in the treatment group (Seftel, Mack, & Secrest, 2004). The testosterone level at which sexual dysfunction occurs is not clear. However, a 2006 study (Marberger, Roehrnorn, Marks, Wilson, & Rittmaster, 2006) found that

the incidence of ED did not begin increasing until testosterone levels fell below 225 ng/dl.

Females

Female sexual dysfunction is marked by lack of desire, painful intercourse, impaired arousal, and inability to achieve orgasm. Approximately 40% of females report sexual concerns (Shifren, Monz, Russo, Segreti, & Johannes, 2008). Interestingly, an evaluation of 1992 data from the National Health and Social Life Survey found that the prevalence of sexual problems in women decreases with increasing age when excluding lubricating troubles (Laumann, Paik, & Rosen, 1999). As compared to men, sexual function in women is less affected by cardiovascular disease. Due to hormonal changes, difficulties with lubrication increase after menopause. The etiology of female sexual dysfunction is often multifactorial, including depression, anxiety, history of abuse, medications, and medical problems causing painful intercourse.

Hypoactive sexual desire disorder is a common sexual disorder in postmenopausal women and has been shown to improve with androgen therapy. This disorder is a chronic absence or decrease in sexual desire that causes personal distress. There is no defined level of testosterone deficiency in women, but testosterone levels decline with age. Testosterone supplementation has been shown to increase sexual desire in postmenopausal women both with and without estrogen therapy (Davis et al., 2008; Simon et al., 2005). However, safety concerns including effects of testosterone therapy on breasts and lipids still require greater investigation.

ROLE OF SLEEP IN SEXUAL DYSFUNCTION

Males

The correlation between OSA and sexual function was described in 1981 (Guilleminault et al., 1981) in a report on patients with OSA. Out of 50 patients with OSA, 44% reported "difficulty having erection and ejaculation". This trend is also reported within those presenting for evaluation for ED. The incidence of OSA within a group of 1025 men presenting for evaluation of ED was 43.8% by overnight polysomnography (Hirshkowitz et al., 1990). These data suggest that the prevalence of OSA in patients with ED is much higher than the general population. This was again described in a prospective review of 401 patients undergoing polysomnography for suspected OSA. Of the patients diagnosed with OSA, 69% reported ED compared to 34% of patients without OSA (Budweiser et al., 2009).

Positive effects of OSA treatment on sexual function were described even before the widespread use of continuous positive airway pressure (CPAP) therapy. As discussed, a 1981 series of 50 patients undergoing tracheostomy for OSA found that 44% of patients reported "difficulty having erection and ejaculation." All but one of the patients reported resolution of these symptoms 6 months after undergoing tracheostomy (Guilleminault et al., 1981).

As CPAP therapy of OSA has become more common, multiple studies have found a significant improvement in ED with CPAP therapy. Goncalves, Guilleminault, Ramos, Palha, and Paiva (2005) compared patients with OSA and ED to age and BMI-matched controls with OSA without ED. Both groups underwent 1-month treatment with nasal CPAP. After treatment, there was no significant difference in ED between groups and 13/17 patients had complete resolution of their ED.

Physiology of Sleep and Sexual Dysfunction Relationship

There are multiple mechanistic hypotheses to explain the associations between sleep-disordered breathing and sexual dysfunction in men. One of the main mechanisms that could explain this relationship is low testosterone (hypogonadism) in men with OSA. This section will explore the effects of sleep apnea on testosterone and sexual dysfunction as well as the role of intermittent hypoxemia and fragmented sleep.

Sleep apnea has been linked to low testosterone levels. However, obesity is a risk factor for both sleep apnea and hypogonadism. Therefore, it is important to try to separate the effects of OSA on testosterone from those of obesity. The correlation between hypogonadism and OSA remains significant in multiple trials after correction for BMI. Testosterone levels were evaluated in 1988 in a group of men with OSA compared to men that snored without OSA. They found significantly lower testosterone levels in the OSA group without a significant difference in BMI (Santamaria, Prior, & Fleetham, 1988). This was confirmed in a study comparing LH and testosterone levels drawn every 20 min during sleep between men with severe OSA and controls without OSA. They found that the nocturnal testosterone rise was significantly lower in the OSA group after correcting for age and BMI. In fact, within the OSA group, the patients with hypogonadal morning testosterone levels had a lower BMI than those not in the hypogonadal range. These findings suggest that this negative effect of OSA on hypogonadism is separate from obesity (Luboshitzky et al., 2002).

The severity of OSA has been shown to positively correlate with the severity of hypogonadism. Eighty-nine severely obese men (BMI $\geq 35\,kg/m^2$) underwent overnight polysomnography and measurement of hormonal parameters. They found a negative correlation between severity of sleep apnea and free testosterone after correction for age and BMI. This correlation was significant for all sleep

parameters, including respiratory disturbance index, minimum oxygen saturation, and time spent below oxygen saturation of 80% and 90% (Hammoud et al., 2011).

The effect of OSA treatment on testosterone levels is not well elucidated. Grunstein et al. (1989) evaluated 45 men with severe OSA. Hormone analysis was performed at baseline and after 3 months of CPAP treatment. They found a significant increase in total testosterone and SHBG after 3 months of CPAP treatment. There was no significant change in weight during this treatment period.

However, this increase in testosterone with CPAP treatment is not supported by the findings of Meston et al. (2003). They performed a parallel placebo-controlled double blind CPAP trial of 101 male patients with moderate to severe OSA. Hormone analysis was performed at baseline and after 1 month of either CPAP or placebo. Interestingly, they found an increase in SHBG in the treatment group, but no change in total testosterone. It is unclear whether these conflicting results are due to treatment length, sample size, sleep apnea severity, or other unknown factors.

OSA results in recurrent hypoxemic episodes during apneas and hypopneas. Severity of nocturnal hypoxemia in OSA correlates with presence of ED. A group of men with OSA and ED were compared to controls with OSA without ED. The men were divided into those with the minimum oxygen saturation >80% and those <80%. ED significantly correlated with lowest oxygen saturation after adjustment for BMI, apnea-hypopnea index (AHI), and age (Goncalves et al., 2005). These findings suggest a direct relationship between degree of hypoxemia and ED that cannot be explained entirely by obesity or severity of OSA.

The physiologic explanation for the association of hypoxemia and ED may be via the effects of intermittent hypoxemia on nitric oxide (NO) induced vasodilation. Animal studies in rats exposed to intermittent hypoxia have found increased vasoconstriction when exposed to an NO antagonist. This suggests that intermittent hypoxia decreases basal levels of NO (Tahawi, Orolinova, Joshua, Bader, & Fletcher, 2001). This theory has also been supported in human studies. NO levels were measured in 21 patients with OSA before and after CPAP therapy. Baseline NO levels were significantly lower in the OSA patients when compared to healthy controls. NO levels significantly increased in the OSA group after two nights of CPAP therapy and remained elevated at 5.5 months (Schulz et al., 2000).

Testosterone suppression has also been correlated to hypoxemia in other respiratory disorders. Serum testosterone levels correlate with severity of hypoxemia in patients with obstructive lung disease (Semple, Beastall, Watson, & Hume, 1980). This same suppression of testosterone has been found in other states of hypoxemia, including pulmonary fibrosis. In a 1984 review of patients with pulmonary fibrosis, it was found that the degree of testosterone deficiency worsened as the hypoxemia worsened (Semple et al., 1984).

The fragmented sleep that is characteristic of OSA may also play a role in sexual dysfunction through its effects on testosterone. The rise in testosterone levels at night can be difficult to differentiate between circadian rhythm and the direct effects of sleep. Therefore, testosterone levels have been evaluated in states of sleep fragmentation (Luboshitzky, Zabari, Shen-Orr, Herer, & Lavie, 2001). Ten healthy males were evaluated under conditions of sleep fragmentation. Sleep fragmentation was accomplished with the 7/13 model (previously described by Lavie, 1987). Every 20 min, starting at 0600, subjects lay down in a dark room and attempted to sleep. After 7 min, they were awoken and stayed awake for the next 13 min. This was repeated 72 times. Testosterone levels were drawn every 20 min from 1900 to 0700 h. They found that the diurnal testosterone rise was blunted in all subjects with sleep fragmentation. In addition, the only subjects that displayed a nocturnal rise in testosterone were those with REM sleep. These findings suggest that the nocturnal rise in testosterone is partly dependent on REM sleep and not circadian rhythm alone. Therefore, the negative effects of OSA on testosterone levels may be due to sleep fragmentation and sleep deprivation.

It has been hypothesized that hypogonadism in OSA is a protective mechanism. This hypothesis is based on the finding that testosterone supplementation may cause or worsen the severity of OSA. While the 2010 Endocrine Society Guidelines (Bhasin et al., 2010) recommend against testosterone therapy in men with severe, untreated OSA, only small trials are evaluating this relationship.

In 1994, a case of a 13-year-old male with Marfan's syndrome and OSA was described. This patient's family noted a significant increase in snoring and daytime sleepiness after starting testosterone supplementation for growth attenuation. Polysomnography and upper airway closing pressure was evaluated at testosterone supplementation peak, trough and 3 months after discontinuing supplementation. Interestingly, his OSA was most severe at peak testosterone supplementation (AHI 44) and normalized after testosterone discontinuation (AHI 2). In addition, upper airway closing pressures improved but did not resolve after stopping testosterone supplementation. This case report suggests that testosterone supplementation may worsen OSA by negatively affecting upper airway collapsibility (Cistulli, Grunstein, & Sullivan, 1994).

A randomized controlled trial with 17 healthy men also supported the findings of negative effects of short-term testosterone replacement on sleep apnea. Half of the men were treated with testosterone injections for 3 weeks while the controls received placebo. Then, after an 8-week washout period, subjects crossed over to the other treatment group. Testosterone was administered in three weekly intramuscular injections of 500 mg testosterone esters (Sustanon 250)

for the first week, then 250 mg for the subsequent two weeks. They found that the testosterone group had shorter total time slept, increased hypoxemia, and increased respiratory disturbance indices (Liu et al., 2003). This suggests that the testosterone caused the worsening of the sleep parameters. However, this study used high-dose testosterone.

To evaluate testosterone doses that would be used in clinical practice, Hoyos, Killick, Yee, Grunstein, and Liu (2012) evaluated the effects of "near-conventional" testosterone supplementation on patients with severe OSA. Testosterone was administered as three intramuscular injections of 1000 mg testosterone undecanoate at 0, 6, and 12 weeks. This testosterone formulation has a more constant release than other formulations to achieve levels near the normal range. They found that testosterone worsened both the oxygen desaturation index and the total amount of nocturnal time with oxygen saturation <90% after 7 weeks. However, these effects were no longer present at 18 weeks.

To further evaluate the effect of testosterone supplementation on OSA, Stewart, Grunstein, Berthon-Jones, Handelsman, and Sullivan (1992) administered androgen blockade to a group of eight men with moderate to severe OSA. They were treated with androgen blockade for 1 week with a significant decrease in testosterone. However, there was no clinically significant change in sleep or sleep-disordered breathing. It is unclear if this lack of change in sleep parameters was due to the short duration of treatment or if there is an alternative explanation for the role of testosterone in sleep apnea.

Females

As compared to men, there is significantly less data evaluating the link between sleep disorders and female sexual dysfunction. Contributing to this lack of data is the difficulty in defining and measuring sexual dysfunction in women.

A 2007 study of 25 women with OSA was one of the first to evaluate the link between sexual dysfunction and sleep disorders in women (Köseoğlu et al., 2007). The women were premenopausal and were divided into groups based on OSA severity. A sexual function questionnaire evaluated desire, sensation, lubrication, orgasm, enjoyment, pain, and partner relationship. They found a positive correlation between sexual dysfunction and OSA severity in all categories except pain and enjoyment. The association between OSA and sexual function in women was also shown in a 2011 study comparing women with OSA to controls from the general population (Petersen, Kristensen, Berg, Giraldi, & Midgren, 2011). They found a significantly higher rate of sexual dysfunction and sexual distress in the OSA population.

The underlying mechanism linking OSA and sexual dysfunction in women is not well elucidated. Possible etiologies include effects on reproductive hormones as well as psychological effects of sleep-disordered breathing.

Stavaras et al. (2012) evaluated 43 premenopausal women and 58 postmenopausal women with OSA. Testosterone, estradiol, and progesterone were measured and sexual dysfunction was evaluated with the Female Sexual Function Index. They found that sexual dysfunction was more common in the women with severe OSA (AHI > 30) when compared to non-severe OSA (AHI 10–30). In the premenopausal women, progesterone had a significant negative correlation with sexual dysfunction. These data support prior studies linking sexual dysfunction with OSA in women. In addition, the authors suggest that progesterone may play a role in this link.

CONCLUSION

The integral role of sleep in many chronic illnesses has become increasingly recognized over the past few decades. Sleep is an important component of reproductive development even during puberty. There is significant evidence linking sleep-disordered breathing to sexual dysfunction. However, as in many other medical conditions, this is an often-forgotten cause. Clinicians should routinely include sleep evaluation in the workup of sexual dysfunction and hypogonadism. In addition, there is a need for additional research in this area to further evaluate the underlying mechanisms as well as treatment options.

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Chapter 13

The Malignant Obesity Hypoventilation Syndrome

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Chapter Outline

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INTRODUCTION

Obesity has become a public health problem in recent decades. One-third of the US population is obese, and the frequency of obesity is increasing worldwide (Flegal, Carroll, Ogden, & Curtin, 2010; James, 2008). The economic impact of obesity is significant due to the associated comorbidities and the increased healthcare utilization of obese subjects. It has been estimated that obesity is responsible for 5–7% of the total annual medical expenditures in the United States (Finkelstein, Ruhm, & Kosa, 2005). The cardiovascular, metabolic, neurologic, and respiratory systems are usually affected by obesity. The respiratory system is compromised in obesity by different mechanisms (see pathophysiology below) and the term obesity hypoventilation syndrome (OHS) has been described as an extreme syndrome characterized by alveolar hypoventilation, chronic hypercapnia and hypoxia, hypersomnolence, polycythemia, and right ventricular failure (Kuchta, 2005). Current estimates suggest that OHS is present in approximately 0.3–0.4% of the population, and that 10–20% of patients presenting to sleep clinics have OHS. (Piper & Grunstein, 2011).

Our group has coined the term malignant obesity hypoventilation syndrome (MOHS) to describe a severe multisystem disease due to the systemic effects of obesity, which is associated with increased healthcare utilization and a relatively high risk of mortality (Marik & Desai, 2013). MOHS seems to be a subgroup of OHS with a worse clinical course and high mortality. Patients with this syndrome have severe obesity-related hypoventilation together with systemic hypertension, diabetes and metabolic syndrome, left ventricular hypertrophy with diastolic dysfunction, pulmonary hypertension, and hepatic dysfunction. In the initial report of the cohort of patients with MOHS, it was shown that all the subjects with this condition had severe multisystem disease directly associated with morbid obesity and 18% patients died in the ICU. These patients had been admitted to our institution on multiple occasions during the previous 2 years (average six admissions in a 2 year period). Seventy-five percent of these patients had been erroneously diagnosed and treated for chronic obstructive pulmonary disease (COPD) and/or asthma and more interestingly, only three patients had been diagnosed with OHS, emphasizing that this disorder is frequently not recognized. Seventy-eight percent of the patients were female and 96% were African–American. The higher prevalence of extreme obesity in African–American women may account for the higher prevalence of MOHS in women.

PATHOPHYSIOLOGY

A review of the mechanisms of the pathogenesis of obesity is out of the scope of this chapter. However, it is important to review the impact that obesity has on different organ systems once it has developed, as it has many clinical implications. The interactions of the multiple organ systems ending in multiple morbidities are complex and not completely understood. In a simplistic way, obesity causes disease by two different mechanisms: the effect of hormones and regulatory cytokines produced by an increased number of

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adipocytes, and the mechanical adjustments associated with increased body mass (Schelbert, 2009).

Hormones, Cytokines, and Metabolic Syndrome

Adipocytes release cytokines (adipokines) as part of their regular physiologic function. Once obesity has developed, this physiologic function seems to be dysregulated, leading to abnormal decreases or increases or both in a number of these adipokines. The most commonly described adipokine abnormalities in pathogenic fat tissue are decreased adiponectin, increased leptin, and increased proinflammatory cytokines such as C-reactive protein, interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α). The abnormal levels of these adipokines are associated with specific metabolic dysfunctions that include insulin resistance, proinflammatory state, excessive fatty acid production, and a procoagulant state.

There is a good evidence to suggest that the development of the aforementioned metabolic dysfunction is correlated with the site of fat deposition rather than only a high body mass index (BMI) (Després et al., 2008). Intra-abdominal or visceral adipose tissue and ectopic fat deposition, which are clinically evident by the abdominal or central obesity, are thought to be associated with dysfunctional adipose tissue. This abdominal obesity is one of the landmarks of the condition known currently as the metabolic syndrome. The metabolic syndrome (also known as syndrome X, insulin resistance syndrome, deadly quartet, or obesity dyslipidemia syndrome) refers to a clustering of risk factors for the development of atherosclerotic cardiovascular disease that include abdominal obesity, atherogenic dyslipidemia, elevated blood pressure, insulin resistance, a prothrombotic state, and a proinflammatory state (Grundy et al., 2004). The metabolic syndrome may be the clinical manifestation of the aforementioned cytokine dysregulation, and it has been determined that patients who have the metabolic syndrome and associated obesity have a 3-fold increase in the risk of coronary artery disease and stroke (Isomaa et al., 2001). In general, development of diabetes is the final outcome of marked insulin resistance (which is prevalent in obese subjects), but is also not uncommonly accompanied by a loss of beta cell function (Burns et al., 2007).

Effects of Obesity on the Cardiovascular System

The cardiovascular system is affected by obesity by a number of different mechanisms. Hemodynamically, obese subjects have an increased peripheral oxygen demand leading to an increase in total blood volume and cardiac output and a decrease in peripheral vascular resistance to meet this increased demand to perfuse more tissue (Alpert, 2001). These hemodynamic changes culminate in left ventricular hypertrophy and a secondary diastolic dysfunction that increases the pulmonary venous pressure. This last aspect along with chronic hypoxemia from hypoventilation (see below) can lead to pulmonary hypertension that eventually may progress to right ventricular failure. The left-ventricular hypertrophy and left-atrial enlargement increases the potential to develop arrhythmias, cardiomyopathy, and other cardiac events. As mentioned, obesity is associated with atherogenesis, which is related to an increased occurrence of coronary events, which may potentially result in systolic dysfunction. Coronary artery disease is also associated with sudden death and arrhythmias.

Effects in the Respiratory System

As previously stated, the obese individual usually has increased oxygen consumption as a consequence of the increased body mass from excess adipose tissue. Meeting this demand is challenging due to an already impaired respiratory system that has an increased work of breathing resultant from decreased lung compliance from fat in the abdominal cavity, the chest wall, and the diaphragm. This increased work of breathing is worsened by an increased airway resistance from decreased lung volumes and by decreased respiratory muscle strength from lack of endurance (Sahebjami & Gartside, 1996). In obesity-hypoventilation subjects, there is a ventilation/perfusion mismatch resultant from these physiologic abnormalities that leads to chronic hypoxemia and hypercapnia.

Obesity has also been implicated as a risk factor for obstructive sleep apnea (Sarkhosh et al., 2013). The odds ratio of developing OSA increases by almost 1.14 with each unit increase in the BMI (Pannain & Mokhlesi, 2010). In addition, obese subjects have an increased risk of venous thromboembolic disease, including pulmonary embolism (Goldhaber et al., 1997; Hansson, Eriksson, Welin, Svardsudd, & Wilhelmsen, 1999). The link between obesity and pulmonary hypertension is less clear. It is thought that the aforementioned conditions (left-sided heart failure, thromboembolic disease, sleep apnea, and hypoxemia from hypoventilation) may lead to a secondary pulmonary hypertension, that left uncorrected may result in right heart failure or cor pulmonale (Friedman & Andrus, 2012).

Effects in the Liver

Insulin resistance is regarded as a hallmark and a causal factor of nonalcoholic fatty liver disease (NAFLD) (Marchesini & Marzocchi, 2007). NAFLD is the most common liver disease in the United States and many parts of the world (Ong & Younossi, 2007). NAFLD encompasses a wide spectrum of clinicopathologic conditions, including simple steatosis and nonalcoholic steatohepatitis (NASH); some individuals with steatosis develop steatohepatitis, a more serious

form of liver damage that may lead to progressive fibrosis, and ultimately to cirrhosis (Diehl, 2010). As with cirrhosis caused by habitual alcohol abuse or chronic viral hepatitis, cirrhosis related to obesity can be complicated by primary liver cancer, both hepatocellular carcinoma and intrahepatic cholangiocarcinoma. Several mechanisms have been postulated to explain the pathogenesis of NASH. Currently, the most favored hypothesis is the "multiple hit." Liver fat accumulation (steatosis) has been suggested as the first hit or the first step resultant from increased lipolysis and free fatty acids. The progression to fibrosis happens after multiple parallel processes (lipotoxicity, increased oxidative stress, mitochondrial dysfunction, iron overload, and proinflammatory cytokines) occur simultaneously leading to NASH, and subsequent hepatic dysfunction (Dowman, Tomlinson, & Newsome, 2010; Duseja & Chawla, 2014; Marchesini & Marzocchi, 2007; Ong & Younossi, 2007).

Effects in the Kidney

The pathogenesis of obesity-related kidney disease can be divided into direct and indirect effects. It is known that obesity is associated with multiple conditions that are known to be associated with increased risk of nephropathy (hypertension, diabetes, hyperuricemia, and multiple sclerosis), which are usually referred as the "indirect effects" (Stenvinkel, Zoccali, & Ikizler, 2013). However, obesity has been found to cause kidney disease and end-state renal disease even after adjustment for these factors, suggesting a direct effect of obesity itself on the kidneys. Although all the direct mechanisms that lead to renal dysfunction are not completely understood and described, there are at least three main pathogenic pathways that have been identified – hemodynamic changes, renin-angiotensin-aldosterone system (RAAS) effect, and adipokine effects—which interact together leading to a common outcome. The obesity-related renal hemodynamic changes are thought to be secondary to increased renal metabolic demand, promoting glomerular hyperfiltration and glomerular hypertrophy leading to proteinuria and glomerulosclerosis. These hemodynamic changes tend to stimulate the RAAS axis, leading to a raised intraglomerular pressure, causing glomerular injury and stimulating the hyperfiltration; eventually, the kidneys start to spill protein in to the urine and begin to undergo permanent irreversible fibrosis. Adipokines, which are proinflammatory, contribute to the capillary hypertension and the fibrosis of the renal parenchyma (Veeraish Chauhan, Chauhan, & Parashar, 2012).

CLINICAL PRESENTATION AND DIAGNOSTIC APPROACH

The original cohort of patients with MOHS was derived from patients admitted with respiratory failure to our intensive care unit. The most common presentation of MOHS is that of progressive hypercapnic respiratory failure, which is frequently caused by an upper respiratory tract infection, pneumonia, or cardiogenic pulmonary edema. Blood gas examination will typically show a very high $PaCO_2$ (up to 100 mmHg), a low PaO_2 (<50 mmHg), a high bicarbonate secondary to chronic CO_2 retention (>28 meq/L), with a low pH because of acute on chronic respiratory acidosis (pH < 7.3). Patients are frequently confused, lethargic, or obtunded because of CO_2 narcosis. Chest imaging usually shows small lung fields often with atelectasis, lobar consolidation, or pulmonary edema. We have defined MOHS as a patient with a BMI > 40 kg/m^2 with awake hypercapnia ($PaCO_2$ > 45 mmHg), the metabolic syndrome, and multi-organ dysfunction. As a rule, MOHS should be suspected in any obese patient presenting with acute respiratory failure.

In general, the diagnostic approach starts by diagnosing OHS in a patient admitted to the hospital or ICU, and the clinical and laboratory investigations are usually focused on identifying triggers that led to the acute episode and the documentation of end-organ damage from MOHS. A suggested diagnostic algorithm for MOHS is provided in (Figure 1). The initial workup should include a regular serum biochemical profile, an echocardiogram, pulmonary function tests (after the acute episode has resolved), and if indicated, further imaging looking at etiologies for liver or renal dysfunction if suggested by chemistries. OHS is usually diagnosed when a patient has obesity (BMI ≥ 30) and has an increased CO_2 after excluding other conditions that may lead to hypoventilation (significant intrinsic lung disease, neuromuscular disorder, or chest wall abnormality) (Piper & Grunstein, 2011). In our initial definition, the patients with MOHS had severe obesity (BMI ≥ 40).

The echocardiogram is a very important diagnostic tool as it provides information on systolic and diastolic function, identifies morphologic abnormalities of the heart, and is a useful screening tool for pulmonary hypertension. In the original MOHS report, and based on the echocardiographic findings, 71% of patients had left ventricular hypertrophy, 61% patients had features of left ventricular diastolic dysfunction, and 77% patients had pulmonary hypertension (defined by a pulmonary artery systolic pressure >35 mmHg). Only a minor proportion of MOHS patients (18%) had systolic dysfunction (left ventricular ejection fraction <50%).

The pulmonary function tests serve two purposes in these patients. First, they help the identification of other potential causes of hypercapnic respiratory failure (e.g., obstructive lung disease like asthma or COPD) and second, they help assess the severity of the restrictive lung defect resultant from obesity. In our group of subjects, none had evidence of obstructive lung disease or evidence of reversible airway disease; however, as mentioned, the

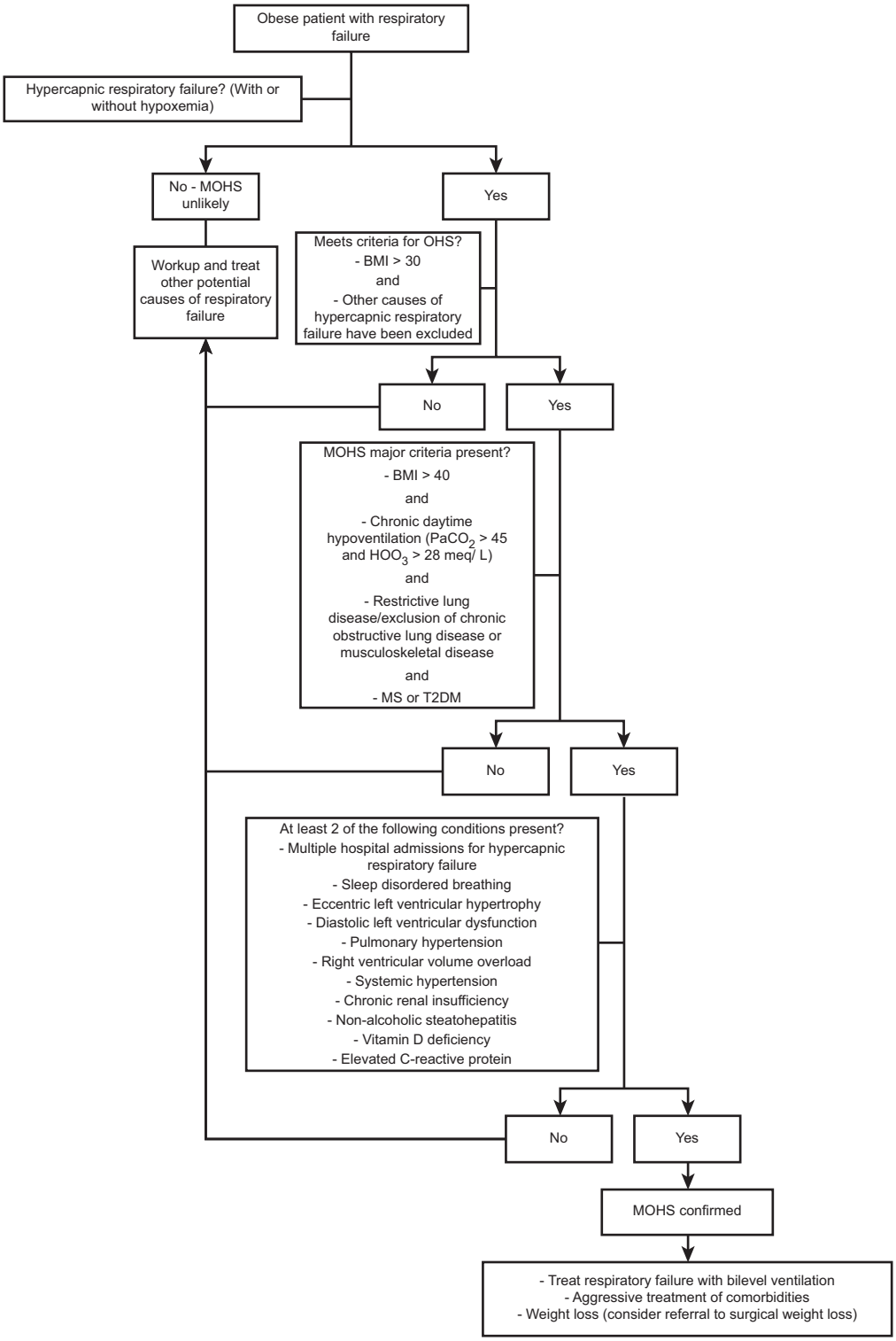

FIGURE 1 Diagnostic algorithm for Malignant Obesity Hypoventilation Syndrome (MOHS).

majority of these subjects had erroneously been diagnosed and treated for COPD or asthma prior to the index admission. MOHS patients tend to have a number of different metabolic abnormalities. All the patients in our cohort had type 2 diabetes and met the criteria for the metabolic syndrome. Furthermore, approximately 40% of subjects had chronic renal insufficiency, 64% had unexplained liver function test abnormalities, all subjects had an elevated

C-reactive protein, and all but one subject had vitamin D deficiency.

MANAGEMENT

The management of patients with MOHS includes the treatment of the episode of acute respiratory failure, and long-term measures to ensure weight loss and decrease the end-organ damage burden from obesity. In the acute phase, the purpose of the therapy is to correct the acute hypercapnia and to treat any triggers for the acute episode. Usual triggers include upper respiratory infection, pneumonia, other infections (urinary tract infection, cellulitis, pancreatitis), and less commonly stroke. Although not present in the initial study, acute coronary syndrome, acute heart failure, and pulmonary embolism should be in the list of possible triggering etiologies in these patients due to their relatively high risk. Management of the hypercapnic respiratory failure is usually performed with mechanical ventilation (either invasive or noninvasive). Noninvasive ventilation (NIV) should always be considered in MOHS patients if there is no contraindication and mental status allows. In our study, the MOHS subjects had elevated intrapleural pressures (the mean intraesophageal pressure as a surrogate of intrapleural pressure was 17 cm H_2O), necessitating a high expiratory positive airway pressure (ePAP) to overcome this pressure. The inspiratory positive airway pressure (iPAP) should be titrated to improve the minute-ventilation of these subjects. There is consensus that a pressure difference between iPAP and ePAP of at least 6–7 cm H_2O is generally required in OHS subjects, but higher pressures may be required to achieve the desired ventilation. With the same rationale, if invasive mechanical ventilation is needed, the positive end-expiration pressure should be high enough to overcome the high intrapleural pressure.

In the long-term phase of management, measures are directed toward weight loss, maintenance therapy with NIV, and management of comorbidities. This requires a multi-disciplinary approach. In terms of weight loss, we advocate for bariatric surgery in patients with MOHS. This recommendation is in line with the 1991 NIH Consensus Development Conference Panel for the treatment of severe obesity, where a recommendation for bariatric surgery was given for individuals who have a BMI greater than 35 kg/m^2 with associated medical comorbidities or whose BMI is greater than 40 kg/m^2 (Gastrointestinal Surgery for Severe Obesity, 1991). Although there has not been a specific trial for weight loss in MOHS patients, it is widely known that surgical therapy is the best-established and most successful method for sustained weight loss in morbidly obese subjects (Smith, Schauer, & Nguyen, 2011). The benefits of surgical treatment of obesity have been documented in multiple publications. Bariatric surgery has been associated with greater long-term weight loss and decreased overall mortality when compared with the medical weight loss treatment (Sjostrom et al., 2007). Also, bariatric operations have resulted in highly significant, reproducible, and long-lasting improvement or remission of type 2 diabetes in severely obese patients (Schauer et al., 2012). Other clinical benefits shown by bariatric surgery have been the improvement of the apnea-hypopnea index in sleep apnea, improvement in the daytime oxygen saturation and improvement of spirometric parameters (Greenburg, Lettieri, & Eliasson, 2009; Lumachi et al., 2010). From the cardiac perspective, bariatric surgery has shown a positive impact by reducing the left ventricle and right ventricle mass and decreasing the right ventricle end-diastolic pressure and pulmonary artery pressures (Garza et al., 2010; Sugerman, Baron, Fairman, Evans, & Vetrovec, 1988; Sugerman et al., 1992). Last, bariatric surgery improves liver and renal dysfunction of morbidly obese subjects (Navaneethan & Yehnert, 2009; Rabl & Campos, 2012). Nonsurgical treatment options in the severely obese population include a combination of low-calorie diets, behavioral therapy, exercise programs, and pharmacotherapy; all of them have limited success achieving weight loss, and when achieved, in long-term follow-up, most patients are unable to maintain their reduced body weight.

NIV is also recommended as a chronic treatment while efforts are made to lose weight. This treatment is likely to improve gas exchange and clinical symptoms and it may improve insulin resistance and hypertension. The maintenance therapy with NIV is difficult. There is a common misconception (in the United States) that a patient who has been initiated on NIV during a hospitalization is unable to receive this device after discharge without a formal polysomnogram (PSG). Although this is true for patients in need of constant positive airway pressure (CPAP) therapy for sleep apnea, our practice has been successful in helping to provide MOHS patients with noninvasive bilevel ventilation devices by documenting a restrictive thoracic defect based on the Centers for Medicare Services' guidelines (Theerakittikul, Ricaurte, & Aboussouan, 2010). However, we always attempt to obtain a formal PSG after hospital discharge using the NIV settings at discharge and titrating these settings during the PSG (under consultation with a sleep specialist). Once the patient obtains a CPAP/BiPAP device, compliance with therapy is frequently poor. Data from the sleep literature suggest that noncompliance is frequently established early in treatment (within the first week of therapy) and that a decline of PAP therapy use in the first few days predicts long-term noncompliance. (Lewis, Seale, Bartle, Watkins, & Ebden, 2004). It is therefore important that measures are taken when this therapy is initiated in the hospital to ensure that the patient is comfortable with the device; these measures include a trial of different types of masks, humidification and warming of the air, and even cognitive therapy.

The management of the other comorbidities requires a multidisciplinary and multispecialty approach. It is important to reduce cardiovascular risk factors by controlling the blood pressure and treating any underlying dyslipidemia based on current guidelines. It is also important to adequately manage the diabetes and its own long-term complications (neuropathy, retinopathy, nephropathy, etc.). As there is an overlap between the management of the hypoventilation itself and the likely coexistence of sleep apnea, we advocate the involvement of a specialized sleep physician in the care of these patients.

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Chapter 14

Obesity, Inflammation, and Obstructive Sleep Apnea: Exercise as Therapy

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INTRODUCTION

Despite the early recognition of the strong association between obstructive sleep apnea (OSA) and obesity, sleep apnea has been treated as a local abnormality of the respiratory tract rather than as a systemic illness. In 1997, it was first shown that the proinflammatory cytokines interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) were elevated in patients with disorders of excessive daytime sleepiness, and it was proposed that these cytokines were mediators of daytime sleepiness (Vgontzas, 2008).

In addition, it was suggested that inflammatory adipokines were elevated in sleep apnea, independently of obesity; however, visceral fat was proposed as the primary link between sleep apnea and obesity. Furthermore, recent findings suggest potential central neural mechanisms for depressed ventilation and consequent development of sleep apnea in obese individuals. Moreover, accumulating evidence provides support for the thesis that obesity via inflammation, insulin resistance, visceral adiposity, and central neural mechanisms plays a major role in the pathogenesis of sleep apnea, sleepiness, and metabolic syndrome (MetS) (Barreiro et al., 2013; Lee, Nagubadi, Kryger, & Mokhlesi, 2008; Vgontzas, 2008; Vgontzas, Bixler, & Chrousos, 2005).

A recent study demonstrated that the severity of OSA is significantly correlated with the severity of MetS and arterial stiffness in obese patients. A large cross-sectional epidemiological study showed that the associations of OSA and metabolic abnormalities were independent of other risk factors. In fact, they showed that subjects with severe to moderate OSA had higher fasting glucose levels, homeostasis model assessment of insulin resistance (HOMAIR) index values, and triglyceride (TG) levels than did the mild and non-OSA group. Indeed, a multivariate regression analysis indicated that an apnea–hypopnea index (AHI) ≥ 15 and time of oxyhemoglobin saturation <90% were independently associated with impaired fasting glucose, elevated TG, and HOMAIR (Togeiro et al., 2013).

Short-term weight reduction therapy improves not only metabolic dysfunction but also the severity of OSA and arterial stiffness, as measured according to the cardio-ankle vascular index (CAVI). Such changes may help to prevent atherosclerosis in obese patients. Finally, the beneficial effect of exercise and weight loss on OSA supports the hypothesis that this kind of therapeutic approach is important to control of these diseases (Iguchi et al., 2013).

OBESITY AS A MAIN RISK FACTOR FOR OSA

OSA is a chronic condition characterized by recurrent episodes of cessation of respiratory airflow, caused by upper airway inspiratory collapse during sleep, leading to significant hypoxemia and periodic arousals from sleep (Vgontzas, 2008; Wolk, Shamsuzzaman, & Somers, 2003). The neurocognitive consequences of repeated arousals are well established, including sleepiness, reduced performance

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in neuropsychological tests, extended reaction times, reduced creativity, decrease in quality-of-life, increased accidents, and metabolic disturbance (Lindberg, Carter, Gislason, & Janson, 2001; Togeiro et al., 2013).

Among the risk factors for OSA, obesity is undoubtedly the most important reversible one. Cross-sectional studies have constantly found an association between increased body weight and the risk of OSA (Lee et al., 2008; Young, Peppard, & Gottlieb, 2002). In fact, obesity is present in approximately 70% of patients with this disorder and it is reaching epidemic proportions (Malhotra & White, 2002). Furthermore, Vgontzas et al. (1994) verified that 40% of obese men presented significant sleep apnea. Consistently, in a population-based prospective study with 690 randomly selected Wisconsin residents, a 10% weight gain predicted an increase of nearly 32% in the AHI, while a weight loss of 10% predicted a 26% decrease in the AHI. Moreover, 10% increase in weight predicted a six-fold rise in the odds of developing moderate to severe sleep breathing disorder (Peppard, Young, Palta, Dempsey, & Skatrud, 2000).

The pathogenesis of OSA involves anatomic factors that favor pharyngeal narrowing, including large neck circumference, cervical soft tissue, vessels, and bony structures (Badr, 1996). Many of these factors promote pharyngeal collapsibility through reducing the caliber of the upper airway or by increasing the pressure surrounding the upper airway (Isono et al., 1997). Although the exact mechanisms underlying the effects of obesity on the risk of OSA are unclear, it is believed that they are related to the effects of fat deposition on airway anatomy or changes in upper airway function (Wolk et al., 2003). A few mechanisms are proposed: (1) decreased pharyngeal lumen size due to fatty tissue within the airway or in its lateral walls; (2) reduced upper airway muscle protective force due to fatty deposits in the muscle; (3) decreased upper airway size secondary to mass effect of the large abdomen on the chest wall and tracheal traction; and (4) changes in central mechanisms regulating airway tone or ventilator control stability (Pillar & Shehadeh, 2008; Wolk et al., 2003).

The proposed mechanisms emphasize that more than weight gain, fat distribution plays an important role in OSA development (Dancey et al., 2003). In fact, reports have highlighted that a thick neck or a large neck is an important variable and correlates better with OSA than body mass index (BMI) (Hoffstein & Szalai, 1993). Dancey et al. (2003) analyzed 499 subjects, and showed that those with a neck circumference higher than 40 cm presented a greater risk (8.4 times) of having OSA. Thus, fat accumulation in the central and neck regions affect more the upper airway size and function when compared to subcutaneous fat accumulation. Hence, obesity is associated with increased upper airway collapsibility (even in nonapneic subjects), with dramatic improvement after weight reduction (Pillar & Shehadeh, 2008).

THE VICIOUS CYCLE BETWEEN OBESITY AND OSA

The interplay between OSA and obesity goes beyond the anthropometrics line. Whereas obesity increases the risk for OSA, sleep apnea may itself predispose individuals to worsening obesity. Patients with recent diagnoses of OSA have a history of excessive recent weight gain in the period preceding the diagnosis (Phillips et al., 1999; Phillips, Kato, Narkiewicz, Choe, & Somers, 2000). OSA consequences include sleep deprivation and sleep fragmentation, and thus an ineffective sleep; and daytime somnolence (Caples, Gami, & Somers, 2005). Together these factors contribute to a fatigue condition favoring sedentary behavior, and thus weight gain (Beccuti & Pannain, 2011). In fact, a cross-sectional study found that increased OSA severity was associated, after controlling for age, sex, and daytime sleepiness, with decreased objectively measured physical activity (Chasens, Sereika, Houze, & Strollo, 2011).

It is well known that one of the abnormalities of sleep architecture seen in OSA is reduced slow-wave sleep. Previously, data demonstrated that experimental suppression of slow-wave sleep, without affecting sleep duration, in young healthy adults lead to increased hunger for calorie-dense foods, with high carbohydrate content, particularly in the afternoon and evening hours (Broussard et al., 2008 cited in Beccuti & Pannain, 2011). The data suggest that not only short hours of sleep but also poor sleep can interfere with eating behavior. Furthermore, the literature has shown that OSA might be associated with changes in neuroendocrine hormones such as leptin, ghrelin, and orexin levels. According to this hypothesis, OSA would be associated with leptin resistance, increased ghrelin and orexin levels, as well as increased appetite and caloric intake (Phillips et al., 2000; Sánchez-de-la-Torre et al., 2011; Spiegel, Tasali, Leproult, & Van Cauter, 2009; Yang, Liu, & Luo, 2013). These hormone alterations may explain alteration in food intake and behavior; however, more studies measuring subjective ratings of hunger, food preferences, or food intake in this population should be performed.

Another possible explanation for changes in eating behavior could be due to alteration in reward-related brain systems (Chaput, 2013). Interestingly, a recent study reported that psychological distress mediates the association between daytime sleepiness and the consumption of sweetened food, highlighting that sleep, mood, and diet are interconnected. One possible explanation would be that individuals who experience daytime sleepiness may consume energy-dense foods to upgrade their energy level or to lighten their negative mood or psychological distress (Moubarac, Cargo, Receveur, & Daniel, 2013). There is

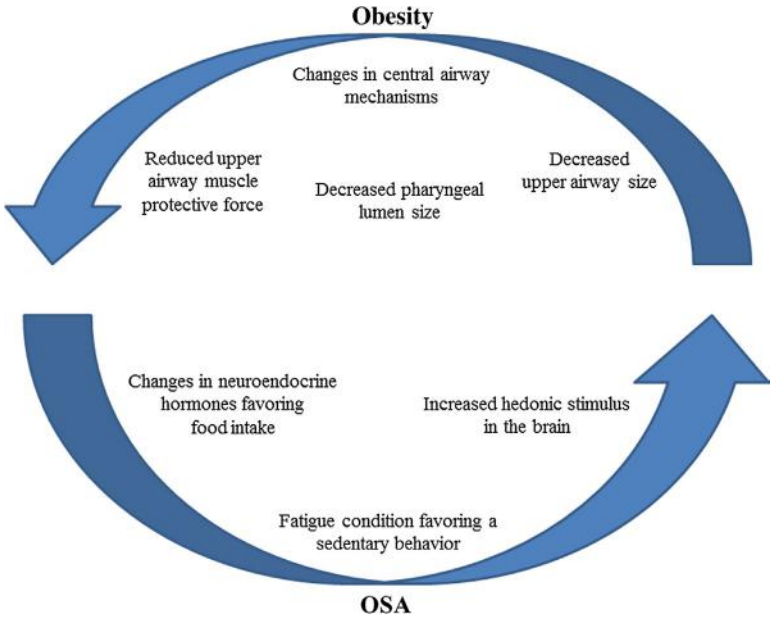

FIGURE 14.1 Vicious cycle between obesity and obstructive sleep apnea (OSA). Obesity would favor OSA through airway anatomy or changes in upper airway function, while OSA would play a role through neuroendocrine mechanisms.

growing evidence in the literature that inadequate sleep increases hedonic stimulus processing in the brain underlying the drive to ingest foods, consistent with the notion that reduced sleep may lead to a greater propensity to overeat (Benedict et al., 2012; Holm et al., 2009; St-Onge et al., 2012).

Together the data suggest that obesity and OSA form a vicious cycle where each results in worsening of the other. Obesity would favor OSA through airway anatomy or changes in upper airway function, while OSA would play a role through neuroendocrine mechanisms, as shown in Figure 14.1.

INFLAMMATION: A COMMON LINK BETWEEN OBESITY AND OSA

Both obesity and OSA share the common link of an inflammatory state. Adipokines are elevated in the obese as well as in patients with OSA, resulting in a systemic low-grade inflammation in both cases (Lee & Pratley, 2005). Chronic inflammation is characterized by infiltration by mononuclear cells, angiogenesis, destruction of the affected tissue, and subsequent healing by replacement through fibrosis. Data clearly indicated that visceral-fat obesity involves all of the landscapes of chronic inflammation (Nishimura, Manabe, & Nagai, 2009).

Increased secretion of inflammatory mediators seen in obese visceral fat reflects the ongoing chronic inflammation of the adipose tissue itself. The adipocyte can secrete inflammatory cytokines, attracting monocytes by monocyte chemoattractant protein-1 (MCP)-1 (Zeyda & Stulnig, 2007). Moreover, a change from an anti- to a proinflammatory phenotype in adipose tissue macrophages has been confirmed in both murine and human obesity (Dâmaso et al., 2011; Lumeng, Bodzin, & Saltiel, 2007; Wentworth et al., 2010). In obese subjects, adipose tissue macrophages show increased expression of TNF-α and inducible nitric oxide synthase, according to the classic proinflammatory activation pattern (M1) (Lumeng et al., 2007).

At the same time studies have shown that OSA is associated with elevated levels of prothrombotic and proinflammatory factors, presenting increased levels of IL-6, IL-8, intercellular adhesion molecule-1 (ICAM-1), MCP-1/C–C chemokine ligand 2 (CCL2), and TNF-α (Carpagnano et al., 2002; Ohga et al., 1999, 2003). The evidence implicated oxidative stress as an important inflammatory activator component in OSA, and has been consistently growing. The repeated breathing cessation, accompanied by drastic changes in oxygen tension, is believed to promote oxidative stress. Thus, this process of hypoxia/reoxygenation would affect cells and cellular components, such as mitochondrial function, which induces increased production of reactive oxygen species (ROS) (Dean & Wilcox, 1993; Lavie, 2003; McCord, 1985; Peng, Yuan, Overholt, Kumar, & Prabhakar, 2003; Suzuki, Jain, Park, & Day, 2006).

Considering that adipose tissue represents a major source for cytokines/adipokines, the cytokines released by adipocytes can pose a problem in recognizing their source: whether they are produced in obesity per se and/or because of OSA (Lavie & Lavie, 2009). However, a recent study submitted wild-type and NADPH oxidase 2 (Nox2) null male mice to sleep fragmentation or sleep control conditions for 3 days to 3 weeks. They showed that oxidative stress pathways were upregulated by sleep fragmentation in visceral adipose tissue, being accompanied by M1 macrophage polarization. Thus, sleep fragmentation, a frequent occurrence in sleep apnea, is a potent inducer

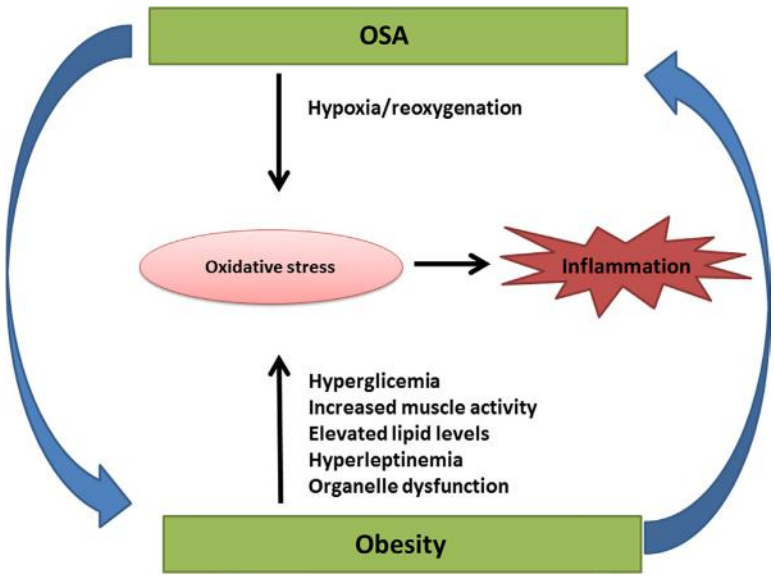

FIGURE 14.2 Both obesity and obstructive sleep apnea (OSA) induce oxidative stress, which will lead to a chronic inflammatory process and create again a vicious cycle. Oxidation stress is believed to be a connecting inflammatory pathway between obesity and OSA.

of insulin resistance via activation of oxidative stress and inflammatory pathways (Zhang et al., 2013). Furthermore, obesity itself contributes to an increase of the oxidative stress through hyperglycemia, increased muscle activity to carry excessive weight, elevated tissue lipid levels, inadequate antioxidant defenses, hyperleptinemia, mitochondrial stress, and endoplasmic reticulum disruption (Codoner-Franch, Valls-Bellés, Arilla-Codoner, & Alonso-Iglesias, 2011; Vincent & Taylor, 2006). Thus, oxidation stress is believed to be a connecting inflammatory pathway between obesity and OSA, once again in a vicious cycle, as shown in Figure 14.2.

OSA AND OBESITY-RELATED DISORDERS

The implications of the association of OSA, obesity, and metabolic pathogenesis have raised considerable interest in the past years. Several studies have investigated the potential independent contribution of OSA to metabolic abnormalities, including diabetes type 2, cardiovascular diseases, and MetS (Bonsignore, Borel, Machan, & Grunstein, 2013).

OSA and type 2 diabetes share the same risk factors (i.e., male, sex, age and central obesity). The prevalence of type 2 diabetes in OSA patients ranges from 15% to 30%, depending on the study and OSA severity (Pamidi & Tasali, 2012). Correspondingly, the prevalence of OSA among patients with type 2 diabetes is high; a study from Sleep Heart Health showed that the prevalence of OSA was 24.0% and 15.6% in patients with and without type 2 diabetes, respectively (Resnick et al., 2003). More recent data by the Sleep Asset Health Dynamics Among the Oldest Old (AHEAD) study indicated that the prevalence of OSA (AHI o15 events/h-1) was 53% in overweight or obese patients with type 2 diabetes (St-Onge, Zammit, et al., 2012). Previously, an observational cohort study examined 1233 consecutive patients and showed that sleep apnea increases the risk of developing diabetes, independent of other risk factors (Botros et al., 2009).

Several studies suggested that sleep breathing disorders are associated with deterioration in insulin sensitivity (Levy et al., 2008; Pamidi et al., 2012; Regazzetti et al., 2009; Yokoe et al., 2008). In fact, Pallayova et al. (2010) showed that OSA was independently associated with altered glucose homeostasis and increased basal beta-cell function in severely obese adults with normal glucose metabolism. Intermediary mechanisms suggested in the deterioration of insulin sensitivity in OSA are induced sympathetic activation, low-grade inflammation, activation of hypothamic–pituitary–adrenal axis, and increased oxidative stress (Bonsignore et al., 2013).

Regarding the impact of OSA on the cardiovascular system, both clinical and epidemiological studies have suggested that OSA may lead to cardiometabolic dysregulation (Marin, Carrizo, Vicente, & Agusti, 2005; Punjabi & Beamer, 2009; Young et al., 2008). Reinke and colleagues showed in their animal model study that OSA exacerbates hypoxia at the tissue level. Hypoxia in the adipose tissue may represent an important role in cardiometabolic dysfunction in OSA (Reinke, Bevans-Fonti, Drager, Shin, & Polotsky, 2011). Hypoxia is a major trigger of lipolysis, dyslipidemia, chronic inflammation, macrophage infiltration, reduction of adiponectin level, elevation of leptin level, adipocyte death, endoplasmic reticulum stress, and mitochondrial dysfunction (Ye, 2009). Obesity itself causes hypoxia in adipose tissue; thus OSA would amplify the hypoxic state (Trayhurn, 2013). Another possible mechanism could be through endothelial dysfunction. Reports have consistently shown that OSA is independently associated with endothelial dysfunction. Namtvedt

et al. (2013) reported a positive association between impaired endothelial function and severity of OSA, independently of obesity and other cardiovascular risk factors. Regarding blood pressure (BP), the results are inconsistent, mainly because increased BP in patients with OSA is multifactorial in origin and may depend on confounding factors. However, recent studies have shown good results of continuous positive airway pressure (CPAP) treatment in reducing BP of patients with OSA (Kartali et al., 2013; Litvin et al., 2013).

MetS is very common, being characterized by a combination of metabolic disturbances (Alberti, Zimmet, & Shaw, 2006). Visceral fat accumulation is the main feature of MetS, also playing an important role in OSA. In fact, Vgontzas et al. (2000) reported visceral fat deposition as the main difference between obese patients with and without OSA. Furthermore, OSA is associated with most components of MetS. Data in the literature reveal that patients with MetS + OSA had higher BP and higher sympathetic drive when compared to those who only presented with MetS (Trombetta et al., 2010). Due to the straight link between MetS and OSA, it had been suggested that OSA may be a component of MetS, thus called syndrome Z (Wilcox, McNamara, Collins, Grunstein, & Sullivan, 1998; Wolk & Somers, 2007). Considering the high prevalence of MetS and its implication on health, researchers have been trying to find the best strategy to decrease and minimize the prevalence and effects, respectively. Data from our group showed that an interdisciplinary approach promoted benefits ameliorating the metabolic biomarkers and improving inflammatory and orexigenic neuropeptides (Corgosinho et al., 2012).

EFFECTS OF EXERCISES AND NUTRITION ON THE TREATMENT OF OBESITY AND OSA

The American Academy of Sleep Medicine recommends the use of CPAP as the main treatment of OSA, this being considered the gold standard procedure; however, it is not well tolerated by some patients (Chasens, Pack, Maislin, Dinges, & Weaver, 2005; Joo & Herdegen, 2007; Kushida et al., 2006). Considering that obesity is a major risk factor for OSA, significant and sustained weight loss, if achieved, is likely to be a useful therapeutic option in the management of OSA, and may be attempted by behavioral programs that focus on aspects such as dietary intervention, exercise prescription for patients, and general lifestyle counseling (Cowan & Livingston, 2012). Therefore, over the past 20 years our research group has investigated the effects of interdisciplinary therapy, including exercise and nutritional counselling, in the control of obesity and its comorbidities, including sleep apnea. In this way, the association of these lifestyle changes provides strong evidence that long-term therapy was effective to improve visceral adiposity, insulin resistance, pro-anti-inflammatory adipokines, the prevalence of hypertension, altered lipid parameters, asthma, cardiovascular diseases, metabolic syndrome, and sleep apnea (Corgosinho et al., 2012; Dâmaso et al., 2013; Masquio et al., 2013; Silva et al., 2012).

Physical exercise in patients with OSA has received increasing attention. It has been shown to be effective in improving OSA as well, decreasing the severity of central sleep apnea in chronic heart failure patients (Ueno et al., 2009; Yamamoto et al., 2007). Researchers have tested the hypothesis that high mass loading effects and OSA constrain the ventilatory response to exercise in morbidly obese subjects as compared to their counterparts without OSA. In an incremental cycle exercise, the functional evaluation included ventilation, oxygen uptake, carbon dioxide production, end-expiratory lung volumes (EELV), inspiratory capacity, heart rate (HR), dyspnea, and leg effort (by a modified Borg scale). In conclusion, the authors suggested that OSA does not limit exercise capacity in morbidly obese subjects. Ventilation contributes to exertion dyspnea similarly in lean subjects and obese patients regardless of OSA (Innocenti, Gigliotti, & Scano, 2012).

Obese patients with OSA and obese controls presented significantly lower VO_2max and VCO_2max values. However, a recent study showed that the respiratory exchange ratio and anaerobic threshold did not differ between groups. Peak diastolic BP was higher among the obese patients with OSA but was not accompanied by changes in peak systolic BP and HR. When multiple regressions were performed, BMI ($P < 0.001$) and male sex in conjunction with diabetes ($P < 0.001$) independently predicted VO_2max (mL/kg/min). The results of this study suggest that obesity alone and sex, when associated with diabetes but not OSA, influenced exercise cardiorespiratory function. This should be considered in the clinical applications of exercise (Rizzi et al., 2013).

Kline et al. (2011) evaluated the efficacy of a 12-week exercise training program (150 min/week of moderate-intensity aerobic activity, followed by resistance training twice/week) for reducing OSA severity and improving sleep quality. They compared with a stretching control group (twice weekly for 12 weeks to perform low-intensity exercises designed to increase whole-body flexibility). Reductions in the AHI and minimum O_2 saturation were achieved when compared with the control group, without a significant decrease in body weight (Ueno et al., 2009). In addition, a prospective randomized controlled trial evaluated the effects of home-based exercise to compare two different training programs. The patients were randomized in three groups: group 1 (aerobic training), group 2 (aerobic with strength training), and group 3 (untrained). Quality of sleep was improved in groups 1 and 2; however, the best results were obtained for group 2, with a significant decrease in the number of apnea and hypopnea events; while in group 1,

only a decrease in hypopnea events was found (Servantes et al., 2012). The main studies with exercise and OSA are presented in Table 14.1.

Recently a systematic review showed that diet plus CPAP had a significant reduction in weight in participants receiving an intensive lifestyle intervention, compared with controls. Reductions were also observed for waist circumference, BMI, and AHI but with high levels of heterogeneity. Thus, they conclude that intensive lifestyle management can significantly reduce obesity indices and improve AHI. Future research is required to investigate this effect due to a limited number of studies identified (Thomasouli et al., 2013).

Moreover, a meta-analysis aiming to evaluate the effectiveness of dietary weight loss in treating OSA among obese patients showed that dietary weight loss programs are effective in reducing the severity of OSA but not adequate in relieving all respiratory events. They selected nine articles representing 577 patients. Dietary weight loss program resulted in a mean BMI reduction of 4.8 kg/m^2. The random-effects pooled AHI indices at pre- and post-dietary intervention were 52.5 and 28.3 events/h ($P<0.001$), respectively. Compared to control, the weighted mean difference of AHI was decreased by 14.3 events in favor of the dietary weight loss programs (Anandam, Akinnusi, Kufel, Porhomayon, & El-Solh, 2013).

Finally, combining diet intervention with physical exercise, another meta-analysis assessed the impact of weight loss on measures of OSA: the AHI and the oxygen desaturation index of 4% (ODI4) index. The study showed that weight reduction programs were associated with a decrease in AHI, with substantial heterogeneity between

TABLE 14.1 Main Studies Aimed to Improve Respiratory Disorders through Lifestyle Intervention, such as Physical Exercise and Nutrition Therapy

Author (Year)	Sample (n)	Intervention	Duration	Results
Foster et al. (2009)	264	Low calorie diet + Exercise control	12 months	The OSA in the intervention group improved, decreasing the AHI from 22.9 (18.0) to 18.3 (15.3), while it worsened in the control group; the prevalence of OSA after one year was half when compared to the control.
Kline et al. (2011)	43	Exercise training (aerobic + resistance training) control	12 weeks	Compared with control, exercise resulted in a significant AHI reduction (32.2 ± 5.6–24.6 ± 4.4) as well as significant changes in ODI ($P=0.03$) and stage N3 sleep ($P=0.03$). Reductions in AHI and ODI were achieved without a significant decrease in body weight.
Sengul et al. (2011)	20	Exercise (breathing + aerobic) control	12 weeks	In the exercise group, no change was found in the anthropometric and respiratory measurements. Whereas significant improvements were found in exercise capacity, AHI, and quality-of-life.
Servantes et al. (2012)	50	Group 1 (aerobic training) Group 2 (aerobic + strength training) Group 3 (untrained)	12 weeks	Improvement in the quality of sleep of groups 1 and 2, demonstrated by a significant decrease in AHI. For group 1, this result was a consequence of a decrease only in hypopnea, but group 2 demonstrated a significant decrease in the number of apnea and hypopnea events. They also experienced decreased nocturnal arousals, associated with a significant increase in sleep efficiency, when compared to control.
Barnes et al. (2009)	12	Very low calorie + exercise (aerobic and resistance training)	16 weeks	Small nonsignificant fall in the AHI. Of the 10 subjects, 6 had a reduction in sleep-disordered breathing, and the AHI was less than 10 in 3 patients. Snoring improved in most subjects.
Norman et al. (2000)	9	Diet + exercise (mainly aerobic)	24 weeks	A significant decrease in the apnea/hypopnea along with improvements in total sleep time, sleep efficiency, number of awakenings/hour, arousals/hour, and apnea index.

AHI, apnea/hypopnea index; OSA, obstructive sleep apnea; ODI, oxygen desaturation index.

studies. They suggested that weight loss through lifestyle and dietary changes results in improvements in OSA parameters, although it is insufficient to normalize them (Araghi et al., 2013).

The possible mechanisms of how nutrition and intervention improve OSA go beyond the weight loss. Iftikhar, Kline, & Youngstedt (2013) indicated that exercise training has a statistically significant effect on AHI that seems to be independent of changes in BMI. They point out the role of strength of respiratory muscles in relation to exercise (Iftikhar, Kline, & Youngstedt, 2013). Our group has massively shown how an interdisciplinary approach can ameliorate the proinflammatory and antiinflammatory profile of obese teenagers. Considering the importance of the inflammatory pathway in OSA and obesity development, an improvement in those parameters may prevent future complications and give a better quality of life (Corgosinho et al., 2012; Dâmaso et al., 2013; Lofrano-Prado et al., 2009; Masquio et al., 2013; Silva et al., 2012).

CONCLUSION AND FUTURE DIRECTIONS

A systematic evaluation of the health standard among obese individuals should be implemented! The emphasis should not be only on the search of appropriate body mass but also on breaking the cycle of obesity, inflammation, and associated respiratory disorders; since emphasizing only one aspect may help, but will have a minor effect compared to prevention and treatment of the three aspects together.

The reduction in body mass itself will help reduce inflammation and respiratory disorders, but surely this will be more effective and faster if there is a combination of treatments for inflammation and sleep disorders as well. A treatment that aims at the main factors tends to be more effective in the challenge of treating obesity, reducing inflammation, and assisting in a full physical and mental recovery during sleep.

Thus, an excellent strategy to combat obesity would be the reduction of body weight through the implementation of healthy lifestyle together with sleep hygiene and improvement of the inflammatory state. To reach a gold standard therapy, the different areas of the health sciences must interrelate and more research in the field should be performed to better understand the complex mechanisms.

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Chapter 15

Obstructive Sleep Apnea in Normal-Weight and Obese Patients

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Depending on age, up to 62% of men and 45% of women in the general population report regular snoring, of which about 5–10% suffer from obstructive sleep apnea syndrome (OSAS) (Ohayon, Guilleminault, Priest, & Caulet, 1997). In a random sample of 602 state employees, 30–60 years of age, in Wisconsin, OSAS, defined as apnea-hypopnea index (AHI) of ≥5 and daytime hypersomnolence, was found in 2% of women (9% with sleep-disordered breathing, 22.6% of whom had hypersomnolence) and 4% of men (24% with sleep-disordered breathing, 15.5% of whom had hypersomnolence) (Young et al., 1993). Several ethnicity-specific epidemiological studies revealed that the prevalence of OSAS is similar in Asian, Indian, Hispanic, and African-American populations (Pillar & Shehadeh, 2008). Obesity is the most important risk factor for OSAS, at least in the Caucasian and African-American populations. The prevalence of overweight (BMI ≥25 kg/m²) and obesity (BMI ≥30 kg/m²) has increased over the past 20 years in several countries around the world, and there has been a corresponding increase in the prevalence of OSAS (Xi, B., Liang, Y., He, T., Reilly, K. H., Hu, Y., Wang, Q., et al., 2012; Befort, C. A., Nazir, N., & Perri, M. G., 2012). A BMI>29 kg/m² increases the risk for OSAS 10-fold, and in morbidly obese patients, the prevalence of OSAS is up to 98%, and two out of three OSAS patients are obese. The relationship between central obesity and OSAS is especially evident in younger adults (Gabbay & Lavie, 2012). While several genetic factors seem to cause a higher risk for obesity, the genetic pathways for OSAS are not as clear. Probably there are regions, like on chromosome 8q, which are linked to both OSAS and obesity (Palmer et al., 2004).

WHAT CAUSES OSAS IN NORMAL-WEIGHT PATIENTS?

People who are not overweight may still suffer from OSAS. The most important general risk factors for OSAS are older age and male gender. The increase in the severity of OSAS with age is more obvious in women and normal-weight men compared to obese men, especially over the age of 35 years (Gabbay & Lavie, 2012). Patient groups where there is a weaker or even an inverse correlation between OSAS and obesity are Asians, children, and patients with craniofacial malformations, severe tonsillar hyperplasia, or pharyngeal tumors. In young Caucasian children, a high BMI z-score does not increase the risk of OSAS. In fact, most children with OSAS are underweight and achieve normal weight after therapy. The positive correlation between BMI and OSAS that is found in adults becomes evident around the onset of puberty at the age of 12 (Kohler et al., 2009). While the prevalence of OSAS in Asians is similar to other ethnic groups, they are more likely to be nonobese. Among 194 Asian patients with OSAS, 63.4% were nonobese and 36.6% were obese (Chirakalwasan et al., 2013).

What is the reason for the development of OSAS in these groups that show a low correlation of OSAS and

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obesity? In children, the main risk factor for OSAS is adenotonsillar hyperplasia, which is most commonly found in children between the ages of 4 and 7 years. This hyperplasia leads to a local narrowing of the pharyngolaryngeal airway and a higher probability of a pharyngeal collapse or stenosis during sleep, leading to a cessation (apnea) or a reduction (hypopnea) of the airflow. Seldom is such a hyperplasia of the tonsils found in adults. Although very rare, adult patients with pharyngeal tumors or a pharyngeal edema after radiotherapy, for example, may develop OSAS due to the accumulation of soft tissue in the pharynx/larynx, which blocks airflow. Another reason for the narrowing of the pharyngeal airway in normal-weight patients is the craniofacial and cervical skeletal anatomy. The craniofacial anatomy i.e., the reduced anteroposterior dimension in Asians, compared to Caucasians is the main reason for the overproportional high risk for OSAS in normal-weight Asians. Therefore, OSAS in Asian men has been found more frequently in nonobese patients compared to nonobese Caucasian male patients. Craniofacial skeletal anatomy can also play a role in the development of OSAS in nonobese Caucasians, although the results of studies vary (Cuccia, Campisi, Cannavale, & Colella, 2007). In some studies the SNB (angle between the lines from the nasion (N) to the sella (S) and N to B (deepest anterior point in the concavity of the mandible)) was smaller in nonobese patients compared to obese OSAS patients, indicating a more retro positioned mandible, while most studies found a shorter cranial base (S–N) and mandible in nonobese OSAS patients (Paoli et al., 2001). Whether the pharyngeal posterior airway spaces at the velar, lingual, and hypopharyngeal planes are smaller in nonobese patients compared to obese patients with similar AHI is controversial.

Beside this anatomical predisposition for the development of OSAS, there are even more important factors that are responsible for the collapse of the pharynx in one patient and not in another with a similar pharyngeal anatomy. These functional factors lead to a deficient reaction of the pharyngeal dilator muscles to negative pressure. A possible reason for this phenomenon is a reduced pharyngeal sensitivity. This means that the negative pharyngeal pressure is not measured sufficiently or that the afferent nerve does not conduct the signal properly. Reduced palatinal two-point discrimination found in OSAS patients supports this hypothesis, although it does not answer the question whether the neurological and probably consequent muscular damage is a reason for the OSAS or if it is caused by repetitive injuries during the obstructive breathing events with its vibrations of the soft tissue (Hagander, Harlid, & Svanborg, 2009). Because the respiratory evoked potentials (cortical reaction on artificial airway occlusions) in OSAS patients compared to healthy controls were reduced only during sleep, not during wakefulness, this seems to be not only a peripheral dysfunction. In addition this reduced cerebral reaction was not only sleep but also respiration specific, since the auditory evoked potentials were normal in OSAS patients (Afifi, Guilleminault, & Colrain, 2003). Sleep fragmentation, which is part of OSAS and is also evident in heavy snoring patients, may also cause a higher collapsibility of the pharyngeal airway, which worsens the sleep-disordered breathing in a kind of circulus vitiosus (Sériès, Roy, & Marc, 1994).

WHAT CAUSES OSAS IN OBESE PATIENTS?

Needless to say, all factors that contribute to OSAS in normal-weight patients are also relevant for obese patients. But the obesity itself may cause or aggravate OSAS by distinct pathways. Fat accumulation, especially in the upper part of the body, which occurs in women after menopause and in men, is associated with a higher risk of OSAS. In patients over 65 years old, the neck circumference correlates better with AHI than central fat mass (measured by dual-energy X-ray absorptiometry) (Degache et al., 2013). In men, neck circumference and abdominal fat explains 17% and 16% of the variance in the AHI, respectively, and together, explain 37% of the variance. In women, fat in the android region (from the top of the ilium superiorly 20% of the distance from the ilium to the body of the mandible), the neck circumference, and BMI are the best predictors of OSAS, explaining 26%, 25%, and 21% of the variance, respectively (Simpson et al., 2010). Fat deposits lead to an increase of upper airway collapsibility via direct and indirect pathways. The accumulation of fat in the neck, especially the submental fat, puts pressure on the pharyngeal structures from outside, mostly in the supine position, while peripharyngeal fat, which is predominantly found posterior and lateral at the palatal level and in the soft palate, directly narrows the pharyngeal lumen mainly in its sagittal dimension (Horner et al., 1989; Li et al., 2012; Shelton, Woodson, Gay, & Suratt, 1993). This narrowed and more anteroposterior-orientated pharyngeal airway is predisposed to partial or complete collapse, leading to hypopneas or apneas. Therefore, the number of apneas and hypopneas correlates with the volume of fat surrounding the upper airway. In addition, compared to nonobese OSAS patients, obese patients have a larger tongue (measured from the most anterior lip of the tongue to the most anteroinferior point of the epiglottic fold), a wider bony nasopharynx, a caudal displaced hyoid bone, and an enlarged soft palate (Yu, Fujimoto, Urushibata, Matsuzawa, & Kubo, 2003). Whether the deeper position of the hyoid bone is more a result of repetitive nocturnal depressions during sleep disordered breathing events, or an anatomic predisposition for OSAS caused by prepharyngeal fat deposits is unclear.

The likelihood of a collapse of the pharynx is increased further by an inappropriate function of the dilating muscles in obese patients, probably due to intramuscular fat deposits

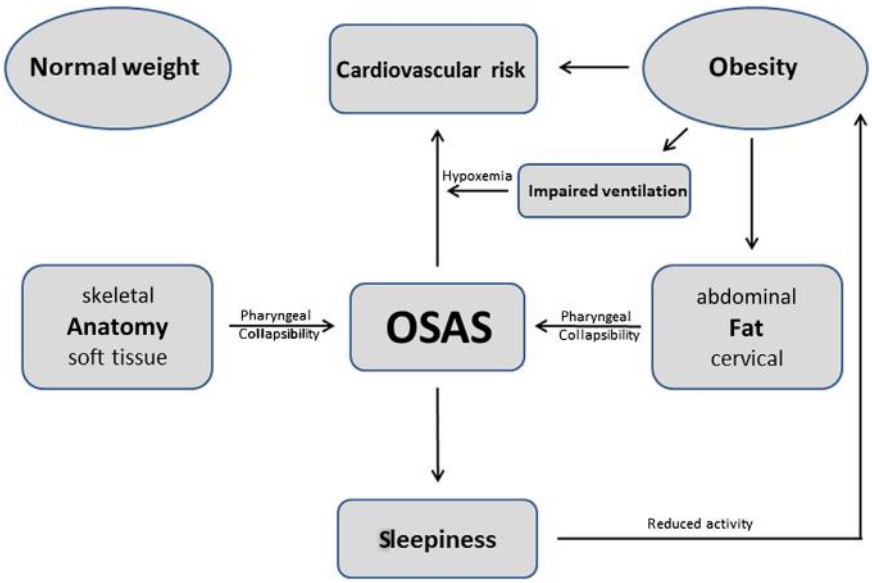

FIGURE 1 Pathophysiology of obstructive sleep apnea syndrome (OSAS) in normal-weight and obese patients.

(Pillar & Shehadeh, 2008). Other studies found no differences in the structure between obese and nonobese patients with OSAS but more type II fibers, which are prone to fatigability, in the musculus genioglossus of OSAS patients compared to controls. Obese patients who also suffer from the metabolic syndrome and congestive heart failure may also experience a rostral fluid shift during sleep, adding to the collapsibility of the pharynx. This fluid shift leads to a peripharyngeal edema and a consequent narrowing of the pharyngeal airway during sleep.

Obesity may also indirectly contribute to the increased collapsibility of the pharyngeal airway in obese OSAS patients. Central obesity causes a cranial displacement of the diaphragm, a reduction of the total respiratory compliance by two-thirds, a reduced functional residual capacity, and an increase of the intra-abdominal pressure. All these factors are correlated with a higher collapsibility of the upper airway, i.e., a higher probability of hypopneas and apneas. Also an artificial abdominal compression during sleep, roughly simulating the effect of augmented abdominal fat, increases the upper airway collapsibility without change of its resistance, whereby the transdiaphragmatic pressure accounts for more than 70% of the upper airway collapsibility (Stadler et al., 2009). A possible mechanism for the higher collapsibility is the reduced caudal traction of the trachea, as this traction has been shown—at least in an animal model—to increase the stability of the pharyngeal airway. A measure of the airway collapsibility is the critical closing pressure, i.e., the pressure when the airway collapses. The higher the closing pressure, the higher the collapsibility of the pharynx. An increase of only 0.5 cm H_2O in the critical closing pressure seems to cause an increase in the AHI of about 10. An increased critical closing pressure of the upper airway in obese patients is also found during general anesthesia, which indicates that this is a mechanical and not only a reflectory effect (Figure 1).

DIFFERENCES IN THE NATURE OF OSAS IN NORMAL-WEIGHT AND OBESE PATIENTS

Obese people consume more oxygen and produce more carbon dioxide. Adipose tissue surrounding the thorax and in the abdomen causes an increase in breathing effort and a restriction of the bronchial ventilation, especially in the supine position. Although obesity per se is not associated with a reduced awake ventilatory chemoresponsiveness, hypoxia may be present in the absence of intrinsic lung disease in morbidly obese patients because of decreased lung volume and ventilation–perfusion mismatching (Mokhlesi, 2010). Morbidly obese patients consume 15% of their oxygen intake for breathing effort, compared to only 3% in nonobese individuals, and therefore, they have to increase their ventilation. The neural respiratory drive and the pressure swings are higher in obese patients and increase further in the supine position, where an intrinsic positive end expiratory pressure is evident (Steier et al., 2009). But the efficacy of the respiratory muscles is reduced. As the upper airway resistance increases during sleep, breathing effort is increased even further, which all together leads to a tendency for increased respiratory effort and hypoxemia in otherwise healthy obese patients. If an obese patient suffers from OSAS, the already disturbed breathing during sleep gets even worse, as the physiological consequences of apnea and hypopnea (like the rise in PaCO2, the fall in PaO2, and the increasing ventilatory effort against an at least partly occluded airway) are added. It, therefore, is not surprising that the higher degree of oxyhemoglobin desaturation during sleep is the main polysomnographic characteristic of

obese OSAS patients compared to their nonobese counterparts (Gabbay, Gabbay, & Lavie, 2012; Peppard, Ward, & Morrell, 2009). There is a linear relationship between BMI and the magnitude of oxyhemoglobin desaturation that is independent of age, gender, sleeping position, baseline SaO2, and breathing event duration. Other measures of body habitus, including neck and waist girth and the waist to hip ratio, were not better predictors of oxyhemoglobin desaturation than BMI. In obese patients, the oxygen desaturation index, therefore, has a higher accuracy as screening for OSAS than in nonobese patients (Ling, James, & Hillman, 2012). Indeed, comparing the polysomnographic findings of 32 normal-weight (BMI <25 kg/m²) and 32 obese (BMI≥ 35 kg/m²) OSAS patients who were matched regarding their AHI, we found a higher apnea index (11.4 versus 6.4, $p=0.04$), a higher minimal (81.3% versus 71.7%, $p=0.003$) and mean (94.9% versus 92.8%, $p=0.007$) oxygen saturation in the normal-weight patients, but a smaller hypopnea index (16.5 versus 21.6, $p=0.047$) and a lower index of snoring (175.2 versus. 394.1, $p<0.001$) than in their obese counterparts (Dreher, Patscheider, & Braun, 2012).

An extreme form of breathing disorder that is by definition found only in obese patients is the obesity hypoventilation syndrome (OHS) (Mokhlesi, 2010). OHS is characterized by an extension of the breathing disorder into wakefulness (PaCO2 >45 mm and PaO2 <70 mmHg). In about 90% of OHS patients, the breathing disorder during the night, which is also part of the definition of OHS, is OSA and in the other 10%, hypoventilation without apneas or hypopneas. About 10–20% of all OSAS patients suffer from OHS, and if the AHI is greater than 60 this percentage increases to 30%. OHS seems to be caused by a defect of the central respiratory drive in combination with an, at least partly, obesity-induced compromised respiratory function (low lung compliance and functional residual capacity, high lung resistance). Like OSAS, OHS occurs in Asians due to craniofacial predisposition in the absence of obesity. Another extreme breathing disorder, but on the opposite end of the scale, which is more commonly found in normal-weight young, and female patients is the upper airway resistance syndrome (UARS). The AHI in UARS is below 5, the diagnostic criteria for OSAS, and oxygen saturation does not fall below 92%. Although there seems to be some overlapping of UARS with the central sensitization syndromes with common symptoms like insomnia, body pain, and irritable bowel, UARS is characterized by respiratory effort-related arousals (Gold, Broderick, Gold, & Amin, 2013). The upper airway collapsibility in UARS patients is lower and the upper airway resistance is higher, probably due to better working protective reflexes of the pharynx, leading to an increased respiratory effort to prevent apneas or hypopneas, compared to OSAS patients. If the respiratory effort becomes too high it triggers an arousal. These arousals supposedly cause the main symptoms of UARS, like fatigue and somnolence (Stoohs, Knaack, Blum, Janicki, & Hohenhorst, 2008).

CONSEQUENCES OF OSAS IN OBESE AND NORMAL-WEIGHT PATIENTS

OSAS is an independent risk factor for cardiovascular disease and is associated with excessive daytime sleepiness, which, in turn, leads to reduced concentration, poor memory, and an overall reduction in performance, posing a safety risk especially while operating machinery or when driving (McNichlas & Bonsigore, 2007; Mediano et al., 2007). This is true for obese and nonobese OSAS patients. Also, in morbidly obese patients, OSAS further increases their already elevated risk for diabetes, hypertension, and impaired heart function. There are also other sequelae caused by OSAS that differ between obese and nonobese patients.

Obesity per se, i.e., in the absence of OSAS, may already cause a worsening of sleep quality by the obesity-associated elevation of humoral factors like tumor necrosis factor-alpha and interleukin-6, but, in these studies, snoring as a possible sign of elevated breathing effort (UARS), for example, has not been sufficiently considered (Resta et al., 2003). In addition, the higher rate of depression, reduced physical activity, or musculoskeletal pain associated with obesity may contribute to a reduced sleep quality in obese patients (Mork et al., 2013; Samartzis, Karppinen, Cheung, & Lotz, 2013).

While obesity is a major risk factor for OSAS, it may also be aggravated by OSAS. Several factors contribute to this circulus vitiosus. The sleep fragmentation caused by the arousals, which terminate the hypopneas and apneas, leads to a disturbance of the humoral equilibrium. There is an imbalance between the appetite-suppressing leptin, which is found to be elevated in most studies but inefficient due to resistance, and its counterpart ghrelin, which was found to be elevated in some studies (Lanfranco et al., 2010; Sánchez-de-la-Torre et al., 2012). Consequently, hunger is increased, which leads to a higher caloric uptake. Another factor leading to weight gain is the reduced physical activity caused by daytime sleepiness, the main symptom of OSAS. Weight gain, reduced physical activity, and higher caloric uptake predispose individuals to insulin resistance and diabetes mellitus. Insulin resistance is also amplified by hypoxia and sympathetic activation that are evident in OSAS (Pillar & Shehadeh, 2008).

The greater severity of intermittent hypoxia in obese compared to nonobese OSAS sufferers may lead to more excessive daytime sleepiness as well as oxidative stress and inflammation, two of the key factors for elevated cardiovascular risk in OSAS patients (Arnardottir et al., 2012; Lavie & Lavie, 2009). In addition, the correlation between OSAS severity and elevated blood pressure, the other key factor for the cardiovascular risk, seems to be stronger in obese

OSAS patients, while some nonobese patients, especially with UARS, even suffer from hypotonus (Guilleminault, Faul, & Stoohs, 2001).

Both OSAS and obesity cause endothelial dysfunction (reduced vasodilation, increased vasoconstriction) by alterations of the vascular structures and reactivity (Lurie, 2011). The negative effect of OSAS and obesity seems to be additive, and is already present in childhood (Bhattacharjee et al., 2012).

Another disorder associated with a higher cardiovascular risk is the metabolic syndrome, which is the combination of central obesity, elevated blood pressure, elevated fasting plasma glucose, and dyslipidemia. While obesity is part of the definition of the metabolic syndrome and its most important risk factor, sleep disturbance seems to be another important cofactor for its development (Nock, Li, Larkin, Patel, & Redline, 2009). OSAS patients have a higher risk for developing the metabolic syndrome, possibly because of the associated sleep disturbance. The combination of sleep disturbance and obesity in obese OSAS patients is another example of a negative synergistic effect of OSAS and obesity, which is not found in normal-weight patients.

Although obesity is not strongly correlated with all case mortality, the combination of obesity and OSAS seems to increase the risk for cardiovascular and metabolic disorders disproportionately (Pillar & Shehadeh, 2008). This increased risk can be seen especially in the extreme form of a breathing disorder and obesity, OHS, with its higher rate of congestive heart failure, angina pectoris, and cor pulmonale compared to uncomplicated obesity or OSAS alone. Therefore, the mortality of untreated patients suffering from OHS was reported to be 7 out of 15 within 50 months (Mokhlesi, 2010).

THERAPY OF OSAS IN OBESE AND NONOBESE PATIENTS

CPAP was first described 30 years ago (Sullivan, Issa, Berthon-Jones, & Eves, 1981). The principle behind this therapy is the application of positive pressure to the upper airway through nasal or oronasal masks. This positive pressure prevents the collapse of the pharyngeal airway due to the otherwise occurring negative pressure below the critical closing pressure during inspiration. CPAP is still the most effective therapy for OSAS and has shown its high potential to reduce the symptoms of OSAS, especially daytime sleepiness, high blood pressure, and other cardiovascular risk factors, and all case mortality (Faccenda, Mackay, Boon, & Douglas, 2001; Marin, Carrizo, Vicente, & Agusti, 2005; Sassani et al., 2004). Therefore, CPAP is the standard therapy for OSAS, and all alternative therapies have to prove their effectiveness and practicality in comparison to CPAP. CPAP is effective in normal-weight and obese OSAS patients (Antczak, J., Horn, B., Richter, A., Bodenschatz, R., Latuszynski, K., Schmidt, E. W., et al., 2012), but the CPAP pressure needed to be effective is, on average, higher in obese patients. BMI, therefore, is an important factor in the prediction formulas of CPAP pressure, which are used in some sleep laboratories to facilitate the selection of the right pressure during polysomnography (Hoffstein & Mateika, 1994). Also, OHS can be sufficiently treated with CPAP in up to 80% of patients (Mokhlesi, 2010). Unfortunately, CPAP therapy does not lead to weight loss in obese OSAS patients (Redenius, Murphy, O'Neill, Al-Hamwi, & Zallek, 2008).

Although the effectiveness of CPAP is high, it is not accepted by all OSAS patients and may not be necessary in mild forms of OSAS. It also may not be the therapy of first choice in patients with correctable abnormalities of the upper airway. As a result, many alternative therapies of OSAS have been developed. An accompanying therapy for OSAS in all obese patients is weight reduction. Weight reduction causes a more caudal position of the cranial displaced diaphragm, an increased functional residual capacity, a reduction of the elevated intra-abdominal pressure, and a stronger tracheal traction. A reduction of the intra- and parapharyngeal fat deposits and improvements in the neuromuscular control reduces the collapsibility of the upper airway and thereby reduces the likelihood of obstructive hypopneas and apneas.(Tuomilehto, Seppä, & Uusitupa, 2013). Unfortunately, the extent of improvement in OSAS with weight reduction seems to be less marked than the worsening of symptoms caused by weight gain. Therefore, even if weight loss cannot be successfully implemented, any further weight gain should at least be prevented. The risk of weight gain also exists and may be even greater for nonobese OSAS patients under CPAP therapy than obese patients. A possible explanation for this phenomenon is a greater decrease in leptin levels in normal-weight patients compared to obese patients during CPAP, which increases appetite and caloric intake (Harsch et al., 2003).

Lifestyle interventions, such as more exercise, are useful for weight reduction and also directly lower the cardiovascular risk (Tuomilehto et al., 2009). The number of steps per day, for example, is inversely correlated with evening blood pressure in overweight OSAS patients, and exercise training alone, i.e., without significant weight loss, already leads to a moderate reduction in AHI and oxygen desaturation (Kline et al., 2011; Mendelson et al., 2013). To enhance weight loss, lifestyle interventions are usually combined with a diet, like the very low calorie diet (VLCD). VLCD is a typically liquid meal diet of 800 kilocalories or less per day containing fatty acids, proteins, and vitamins but no or very few carbohydrates, which should induce a weight loss of about 2 kg per week. The weight loss achieved by lifestyle intervention and diet was reported to be between 3% and 18%. This weight reduction was associated with a reduction in the AHI in obese patients that ranged between 3% and 62% (Tuomilehto et al., 2013). Thus, weight reduction can be more successful in some patients and may

also be more beneficial in some patients than others in terms of lowering the AHI.

Bariatric surgery (gastric banding or bypass, sleeve gastrectomy) is more effective in weight reduction (12–72%) and improvement of AHI (48–98%) in obese patients with OSAS. In a sample of 161,756 patients with a BMI of 45.62 kg/m² or greater, the mortality within/after 30 days after bariatric surgery was 0.008%/0.31%, the complication rate was 17%, and the reoperation rate was 7% (Chang et al., 2013).

Another therapeutic option for mild and supine position-dependent types of OSAS is positional therapy. An example of this kind of therapy is the use of specially formed vests with prominent pads at the back, which should prevent the patient from sleeping in the supine position. A reduction in AHI of at least 50% by lateral compared to supine sleep position was reported in 91% of normal weight patients and in 57% of obese patients (Itasaka, Y., Miyazaki, S., Ishikawa, K., & Togawa, K., 2000). Therefore, positional therapy seems to be more effective in nonobese than in obese OSAS patients.

Oral appliances are an alternative conservative therapy for OSAS. The aim of the oral appliances is to prevent the collapse of the pharynx by repositioning the mandibula, the tongue, and the soft palate and activating the dilatoric muscles. There are two main categories of oral appliances, the tongue retaining appliances, which attempt to hold the tongue in a forward position using a suction bulb, and the better-studied mandibular repositioning appliances, which are fitted to the teeth of the mandibula and the maxilla and keep the mandibula in a protruded position. This protruded position of the mandibula prevents the tongue and other oral and pharyngeal soft tissues from falling back during sleep. Many patients prefer oral appliances to CPAP, and the effects on the symptoms of OSAS seems to be similar. But, because the success rate of oral appliances is lower than that achieved by CPAP and in most studies negatively correlated with obesity, it is more an option for normal-weight patients with mild to moderate OSAS. The response rate of oral appliance treatment in Asian OSAS patients, for example, was 52% in nonobese and 25% in obese patients (Tsuiki et al., 2013).

While bariatric surgery has, as discussed, a more indirect influence on the collapsibility of the pharynx, it is of course also possible to reshape the pharyngeal airway by direct surgery to prevent it from collapse during sleep. Surgery on the upper airway as a second line therapy is an option if the conservative therapies are not accepted by the patient or are not effective (Randerath et al., 2011). Surgery as first-line therapy should be considered if there is a clear pathology of the upper airway likely causing OSAS and which can be cured by surgery with an acceptable risk. Examples of first-line surgery in OSAS are the adenotonsillectomy in severe adenotonsillar hyperplasia or resections of an OSAS-causing pharyngeal tumor. In cases where surgery is chosen as a second-line approach, risk should be minimized by using a minimally invasive procedure. Examples of minimally invasive surgery are interstitial radiofrequency therapy of the palate, the palatine tonsils, and the tongue, or soft palate implants, which are mainly recommended for primary snoring and mild OSAS. In moderate and severe OSAS uvulopalatopharyngoplasty, tonsillectomy, hyoid suspension, partial resection of the tongue, tongue suspension or genioglossus advancement are used.

The reported surgical success rate (reduction of AHI by at least 50% and less than 20) of surgical interventions (without tracheostomy and maxillomandibular advancement) decline from about 60% in patients with a BMI of less than 30 kg/m² to 30% in patients with a BMI between 30 and 35 kg/m² and to less than 5% in patients with a BMI of more than 35 kg/m² (Verse & Hörmann, 2011). Therefore, and because of the higher risk of perioperative morbidity and complications, these kinds of surgery are generally not recommended for patients with a BMI of more than 30 kg/m². The reduced effectiveness of surgical treatment in obese patients is already evident in children: 60% of nonobese children suffering from OSAS are cured by adenotonsillectomy, while only 24% of the obese children are cured after surgery (Gozal, Capdevila, & Kheirandish-Gozal, 2008). Also, revision surgery, including, for example, lingual tonsillectomy, failed more often in obese children compared to nonobese children (Chan, Jan, & Koltai, 2012).

In severe cases of OSAS, maxillomandibular advancement and tracheostomy—the first described effective therapy of OSAS—may be applied. However, mostly because of the stigmatization and the permanent impairment of quality of life associated with a tracheostomy and the effectiveness of other therapeutic options, this more drastic surgical procedure is now only seldom performed for the treatment of OSAS. It works as a bypass for the collapsible pharyngeal airway and cures OSAS, according to most studies, in more than 90% of patients. In a more recent study, eight of 10 obese OSAS patients (BMI 36 kg/m²) tolerated the tracheostomy tube for more than 6 months, but only four of them were complete responders, i.e., showed a reduction of their oxygen desaturation index below 5 (Browaldh, Markström, & Friberg, 2009). Despite a normalization of the Epworth sleepiness scale score in all patients, five patients still had pathological oxygen desaturations. The nonresponders had the highest BMI and probably suffered from comorbidities like OHS that required additional mechanical ventilation. Maxillomandibular advancement surgery is regarded as the most effective surgical treatment, other than tracheostomy, of OSAS. It consists of a maxillary Le Fort I osteotomy, a bilateral mandibular osteotomy, and a fixation of the segments, on average, 1 cm anteriorly, which leads to an increase especially in the anteroposterior dimension of the upper airway (Hochban, Brandenburg, & Peter, 1994).

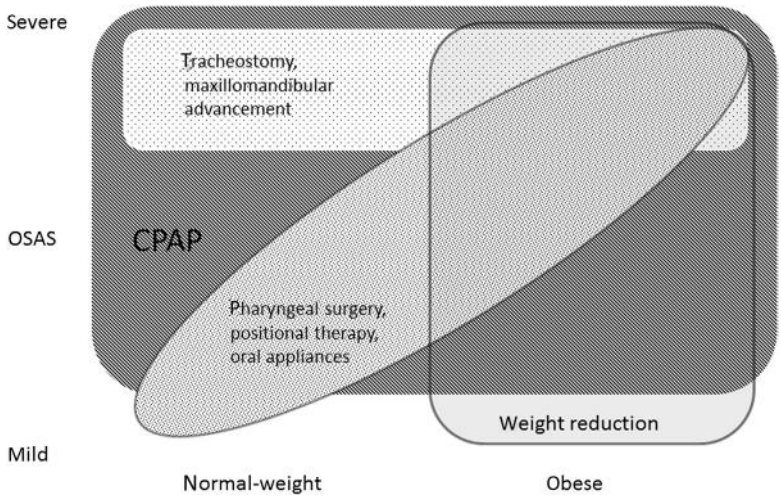

FIGURE 2 Therapy of obstructive sleep apnea syndrome (OSAS) as a function of severity and weight.

The success rate (reduction of the AHI of more than 50%) of the maxillomandibular advancement is up to 90% and is, as far as the studies considered the effect of BMI, similar in obese and normal-weight OSAS patients. In patients with maxillomandibular deficiencies, for example, severe mandibular retrognathy, who refuse CPAP treatment, maxillomandibular advancement surgery may be considered as a first-line surgical procedure. Otherwise it is part of a multilevel therapeutic concept and an option for patients who have already had less invasive soft tissue surgery without sufficient effect (Li et al., 2000) (Figure 2).

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Part III

Metabolic Syndrome and Sleep Deprivation

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Chapter 16

Obstructive Sleep Apnea and the Metabolic Syndrome: Clinical Profiles and Relationships

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TERMINOLOGY OF SLEEP APNEA

Apnea in adults is defined as cessation, or near cessation, of airflow for at least 10 s (Iber, Ancoli-Israel, & Chesson, 2007). Hypopnea is less precisely defined: simply put, it is a decrease in airflow that does not meet the criteria for apnea.

Sleep-disordered breathing has traditionally been classified into *obstructive sleep apnea (OSA)*, where obstructive apneic events predominate (characterized by respiratory efforts against a closed, or nearly closed, upper airway); and *central sleep apnea*, where central apneic events predominate (characterized by absent or markedly reduced respiratory efforts in the presence of a patent central airway). A *Mixed apnea* begins as a central apnea and ends as an obstructive apnea. *Complex sleep apnea* or *treatment emergent sleep apnea* is characterized by the emergence or increase in central apneas and hypopneas when continuous positive airway pressure therapy (or bilevel positive airway pressure without a backup respiratory rate) is initiated for OSA. Complex sleep apnea has been regarded as a form of OSA, though this view is by no means universal (Malhotra, Bertisch, & Wellman, 2008).

The *upper airway resistance syndrome* (UARS) is characterized by the absence of significant apneas and hypopneas, although snoring, flow limitation, and exaggerated inspiratory efforts may be prominent. It is diagnosed in the presence of an excess of respiratory effort-related arousals. UARS has nevertheless been subsumed under OSA in the most recent edition of the International Classification of Sleep Disorders (*Diagnostic and Coding Manual*, 2005).

The Apnea-Hypopnea Index (AHI), or the number of apneas and hypopneas per hour of sleep, is a measure of severity of sleep apnea.

THE METABOLIC SYNDROME

The metabolic syndrome (MS) is the simultaneous occurrence of hyperglycemia (or insulin resistance) and two or more related metabolic abnormalities such as elevated blood pressure, dyslipidemia, central obesity, or microalbuminuria (Alberti & Zimmet, 1998).

MS is associated with an increased risk of morbidity and mortality (Lakka et al., 2002). It also appears to be a marker for OSA (Lam et al., 2006). The association of OSA with MS has been referred to as syndrome Z (Wilcox, McNamara, Collins, Grunstein, & Sullivan, 1998). Indeed, syndrome Z has come to be regarded as an extended form of MS

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(Vgontzas, Bixler, & Chrousos, 2005), and appears to have a more powerful impact on atherosclerotic cardiovascular morbidity than has MS itself (Drager et al., 2009), multiplying rather than merely adding to the associated risks (Venkateswaran & Shankar, 2007).

A shortened total sleep time can predispose one to glucose intolerance and insulin resistance (Spiegel, Knutson, Leproult, Tasali, & Cauter, 2005). Impaired glucose metabolism is a feature of OSA, and this effect appears to be independent of obesity (American Diabetes Association, 2009). The prevalence of OSA in patients with type 2 diabetes mellitus ranges between 23 and 75% (Tasali, Mokhlesi, & Van Cauter, 2008). On the other hand, about 60% of patients with OSA are diabetic (Hasan, Uzma, Swamy, Shoba, & Kumar, 2012); in these patients, insulin resistance appears to directly correlate with the AHI (Punjabi et al., 2004). OSA appears to predispose to MS (Lévy, Bonsignore, & Eckel, 2009). In fact, it has been proposed that OSA develops in a sequential manner atop the metabolic syndrome (Sharma & Sreenivas, 2010).

PRIMARY SNORING

Snoring is the sound produced by vibration of the soft tissues of the upper airway during sleep. Although almost all individuals snore occasionally, more than 40% of males and about 30% of females snore *habitually* (Young et al., 1993). Primary snoring (simple snoring, benign snoring) which, by definition, produces little or no fragmentation of sleep, lies at one end of the spectrum of snoring (see Figure 1). At the other lies the most severe form of OSA, where so severely is the airway compromised during sleep, that breathing and sleeping at the same time is almost impossible.

Although by implication, *primary snoring* is harmless, it has been shown to predispose to carotid artery atherosclerosis by the transmission of vibration from the adjacent airway (Lee et al., 2008). Contrary to evidence presented by some earlier studies (Norton & Dunn, 1985; Koskenvuo et al., 1987), primary snoring does not in fact appear to increase the risk of systemic hypertension (Hoffstein, 1994) or of cardiovascular or cerebrovascular mortality (Marshall, Wong, Cullen, Knuiman, & Grunstein, 2012). However, there is emerging evidence that snoring can increase the risk of subsequent development of diabetes (McArdle, Hillman, Beilin, & Watts, 2007; Otake et al., 2009), and it has been suggested that screening for sleep apnea be performed when fasting hyperglycemia exists against a background of snoring (Shah, Bang, & Bhagat, 2010).

With the currently available evidence, however, treatment of snoring specifically for the prevention or control of hypertension or of ischemic heart disease does not appear to be warranted (Jennum, Hein, Suadicani, & Gyntelberg, 1995; Trotter, D'Souza, & Morgan, 2003).

AIRWAY PHYSIOLOGY IN OBESITY

As many as 80% of all individuals with polysomnographically diagnosed OSA are obese; conversely, at least 65% of obese individuals have OSA (Hasan et al., 2012). By altering respiratory mechanics, obesity can adversely impact lung function and amplify the effect of lung disease.

The upper airway is a complex structure that serves conflicting demands: it needs to remain patent for ventilation, but is required to collapse during deglutition and perform complex motor behaviors during vocalization. The human hyoid cartilage, unlike that of many lower mammals, is not anchored to the styloid processes of the skull (Morgan & Remmers, 2007). Thus the human pharynx, having no rigid support (except at its uppermost end, which is attached to bone, and its lower end, which is attached to the cartilages of the larynx), is inherently collapsible; its patency depends on the coordinated function of more than 20 skeletal muscles that serve as pharyngeal dilators (Young & McDonald, 2004). In obese individuals, the pharyngeal airway is compromised in its anteroposterior diameter (Huang, White, & Malhotra, 2005) (due to enlargement of the soft palate and tongue), but also, rather more substantially, in the lateral plane (due to thickening of the lateral pharyngeal walls) (Schwab et al., 1995). Narrowing of the upper airway is largely due to an increase in parapharyngeal adiposity, and

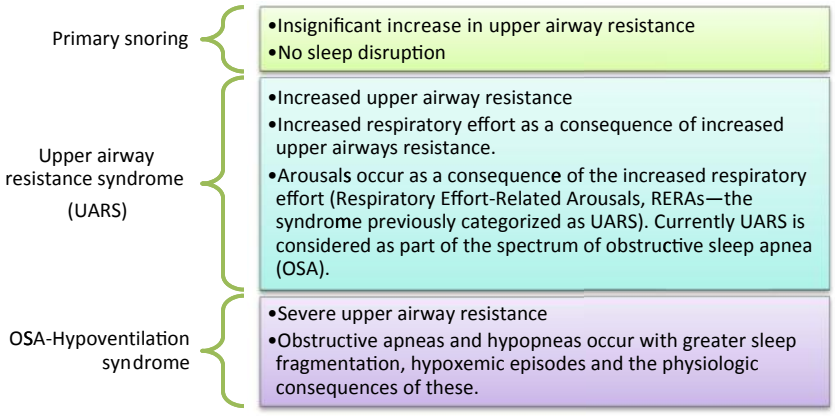

FIGURE 1 Spectrum of obstructive sleep disordered breathing.

to a lesser extent, to an increase in fat-free muscular tissue within the pharyngeal walls (Huang et al., 2005; Sériès et al., 1995).

During sleep, in obese individuals, the increased abdominal adiposity and the supine posture act together to result in a significant reduction of lung volumes, which in turn reduces the "tracheal-tug" or the downward pull exerted on the trachea during diaphragmatic descent. This results in a further increase in the thickness of the lateral pharyngeal walls (Van de Graaff, 1988) promoting airway collapse, especially at the level of the velopharynx (Tagaito, Isono, Remmers, Tanaka, & Nishino, 2007).

Obesity and Lung Function

The surplus of adipose tissue that lies about the rib cage, as well as in and around the abdominal cavity, can limit chest expansion and thereby reduce functional residual capacity (FRC) in direct proportion to the body mass index (BMI) (Pelosi et al., 1998). Even a relatively slight increase in BMI is capable of impacting upon the FRC (Jones & Nzekwu, 2006), and in exceptionally obese individuals, FRC can actually approach residual volume. A markedly decreased FRC will promote airway closure at low lung volumes (especially in the dependent zones of the lung) with consequent expiratory flow limitation.

Obesity has a somewhat less pronounced effect at the extremes of lung volume: marked obesity will result in a relatively trivial decrease in total lung capacity (Jones & Nzekwu, 2006). In comparison to peripheral or lower body obesity, central (visceral, abdominal) obesity seems to have a more substantive influence on the forced expiratory volume in the first second (FEV_1) as well as on the forced vital capacity (FVC) (Lazarus, Sparrow, & Weiss, 1997).

Interestingly, a decreased FVC (that is, a restrictive defect in lung function) has been correlated with insulin resistance (Nakajima et al., 2008), as well as with type 2 diabetes mellitus and MS (Ford, Mannino, & National Health and Nutrition Examination Survey Epidemiologic Follow-up Study, 2004). Reduced lung function has been implicated as a player in cardiovascular morbidity (Hole et al., 1996; Scarlata, Luca Fimognari, Moro, Pastorelli, & Antonelli-Incalzi, 2010; Schünemann, Dorn, Grant, Winkelstein, & Trevisan, 2000; Sin, Wu, & Man, 2005), and the presence of MS appears to magnify the risk (Leone et al., 2009; Scarlata et al., 2010). Both reduced FVC and FEV_1 correlate with cardiovascular morbidity (Schünemann et al., 2000; Sin, Wu, & Man, 2005).

Although there is an apparent increase in respiratory system resistance on account of airway narrowing (Yap, Watson, Gilbey, & Pride, 1995), the specific airway resistance (which takes into account lung volumes) has been shown to be normal (Nicolacakis et al., 2008). On the other hand, obesity does appear to genuinely impact *small* airway function (Rubinstein, Zamel, DuBarry, & Hoffstein, 1990; Zerah et al., 1993). Small airway dysfunction can persist in spite of weight loss: this argues for the presence of structural airway remodeling, rather than an indirect mechanical effect on airway diameter alone. It has been hypothesized that cyclical and repetitive opening and closing of unstable small airways promotes lung dysfunction in a manner analogous to the atelectrauma of acute respiratory distress syndrome (Milic-Emili, Torchio, & D'Angelo, 2007). The prevalence of MS was shown to be much higher in patients with airflow obstruction in one study (Lam et al., 2010), and again this relationship was strongest with the central type of obesity.

Obesity is associated with reduced tidal volumes and a rapid, shallow pattern of breathing (Sampson & Grassino, 1983) that typically occurs with elastic loading (Axen, Haas, Haas, Gaudino, & Haas, 1983): this presumably reflects the decreased compliance of the respiratory system. Experimentally, resistive or elastic loading of the airway has been shown to provoke a prompt increase in ventilation during wakefulness; during sleep, imperfect compensatory mechanisms can result in hypoventilation until chemoreceptor output increases (Iber, Berssenbrugge, Skatrud, & Dempsey, 1982).

In exercising obese subjects, tidal volumes remain relatively unchanged; it is rather the increase in respiratory rate that likely contributes to the perception of dyspnea (Ofir, Laveneziana, Webb, & O'Donnell, 2007).

Obese subjects can be hypoxemic during tidal breathing at rest as a consequence of premature airway closure, and even mild obesity is capable of widening the alveolar-arterial oxygen difference (Jenkins & Moxham, 1991). Indeed, in patients with OSA, MS has been shown to be a stronger predictor of nocturnal desaturation than AHI (Takama & Kurabayashi, 2008).

Increased visceral fat is capable of increasing intra-abdominal pressure (Sugerman, 2001), and this can have implications for diaphragmatic function (Hudgel & Devadatta, 1984; Sharp, Druz, & Kondragunta, 1986). Despite working against a poorly compliant chest wall and increased airway resistance, the maximum inspiratory and expiratory pressures generated at all lung volumes are actually lower, and not higher, compared to those in nonobese individuals (Kelly, Jensen, Elliott, & Crapo, 1988). In those obese individuals with obesity hypoventilation syndrome (OHS), this difference was actually greater (Koenig, 2001; Ray, Sue, Bray, Hansen, & Wasserman, 1983). Nevertheless, obese subjects, even during tidal breathing, do incur a substantial cost of breathing (Koenig, 2001). It is conceivable that the additional load imposed by the adiposity results in overstretching of the diaphragmatic muscles, altering length-tension relationships: predictably, diaphragmatic response worsens in the supine position with the loss of the gravitational advantage (Sharp, Druz, & Kondragunta, 1986).

A decreased ventilatory reserve makes such patients vulnerable to respiratory failure with relatively minor infectious or inflammatory insults. Marked obesity is also associated with prolonged mechanical ventilation and delayed weaning (El-Solh, Sikka, Bozkanat, Jaafar, & Davies, 2001; Akinnusi, Pineda, & El Solh, 2008).

PULMONARY VASCULATURE

It appears that in obese individuals, there is an increased deposition of fat within the pulmonary vasculature (Kodolova & Lysenko, 1979; Lysenko, 1990; Reinilä, Koivisto, & Akerblom, 1977), but it is as yet unclear what impact on lung function this might have. The angiopathy of diabetes mellitus can affect the pulmonary capillary bed, albeit to a smaller extent than it can the capillary systems elsewhere in the body (Kodolova & Lysenko, 1979). The changes of diabetic microangiopathy have in fact been demonstrated within the capillaries and arterioles of the alveolar septa and pleura (Foster, Ravikumar, Bellotto, Unger, & Hsia, 2010), but the significance of this is uncertain. In animal models, lipid deposition has been observed within alveolar macrophages as well as in type II pneumocytes (Brown & Longmore, 1986; Lysenko, 1990), with foreseeable implications for surfactant function (Inselman, Chander, & Spitzer, 2004).

In obesity, the pulmonary blood volume is increased, and probably plays a part in decreasing the lung compliance (Weyman et al., 2002) as well as in exacerbating the pulmonary arterial hypertension that occurs in severe OSA/OHS.

Pulmonary venous hypertension (PVH) commonly accompanies OSA, especially when OHS and MS coexist (Robbins et al., 2009). In animal models of MS, hyperglycemia itself has been shown to contribute to PVH by diminishing the production of nitric oxide in the pulmonary circulation (Marchesi, Ebrahimian, Angulo, Paradis, & Schiffrin, 2009).

THE OBESITY HYPERVENTILATION SYNDROME

OHS is defined when daytime hypercapnia ($PaCO_2 > 45$ mmHg) exists in the presence of clinical obesity (BMI> 30 kg/m^2), in the absence of other causes of hypoventilation (Piper & Grunstein, 2011) Obesity is a major player in the pathogenesis of OHS.

A minority of subjects with OSA—about 11%—have OHS (El-Gamal, Khayat, Shikora, & Unterborn, 2005), but a majority (80–90%) of patients with OHS have OSA (Olson & Zwillich, 2005). Although OSA and obesity hypoventilation syndrome (OHV) share many physical characteristics, OHS patients as a rule are usually more obese, have higher AHIs, and have more profound oxygen desaturation than those OSA patients who do not manifest OHS. Compared to individuals with OSA alone, the relatively severe nocturnal hypoxemia and hypercapnia that occur in patients with OHS can result in greater sympathetic activation and oxidative stress, and greater cardiovascular morbidity (Teichtahl, 2001).

Precisely why daytime CO_2 retention develops in some obese OSA patients but not in others is unclear; it is possible that diminished central respiratory drive, repetitive airway obstruction during sleep, abnormal load responsiveness, ventilatory muscle dysfunction, increased work of breathing, and increased CO_2 production are all operative to varying degrees. Clearly, an augmented respiratory drive in normocapnic obese individuals appears to compensate for the mechanical loading that occurs on account of obesity (El-Gamal et al., 2005). In those individuals who go on to develop OHS (Teichtahl, 2001), there is increasing speculation that leptin resistance underlies the impaired central control of ventilation. Leptin is an adipokine that serves the physiologic function of appetite suppression (and prevents excessive weight gain): it possibly plays an important role in the preservation of minute ventilation in obese individuals. (O'Donnell et al., 1999). In leptin-deficient obese mice, the ventilatory output in response to hypercapnia was demonstrably reduced: in these animals, the ventilatory drive could be restored with leptin administration (O'Donnell et al., 1999). It is possible that increased leptin levels represent a compensatory mechanism that enables obese subjects to remain normocapnic (Lévy et al., 2008). As well, leptin conceivably plays an important role in the determination of the types of muscle fibers in the diaphragm (Tankersley et al., 1998).

Patients with OHS actually exhibit increased leptin levels, probably on account of tolerance to the effects of leptin (Makinodan et al., 2008) either as a result of decreased penetration into cerebrospinal fluid (Caro et al., 1996) or because of resistance at the level of the central receptor (Malli, Papaioannou, Gourgoulianis, & Daniil, 2010). Indeed, leptin levels seem to predict hypercapnia better than the degree of obesity itself does (Redolfi et al., 2007). Leptin levels have been shown to decline remarkably after initiation of CPAP therapy (Chin et al., 1999).

Noninvasive ventilation is the treatment of choice in individuals with OHS: since positive airway pressure most often normalizes or improves ventilatory responsiveness to chemostimuli, it is tempting to speculate that the decreased ventilatory responsiveness may be a consequence rather than a cause of OHS (Redolfi et al., 2007).

THE OVERLAP SYNDROME: COPD AND OSA

The co-occurrence of chronic obstructive pulmonary disease (COPD) and OSA has been referred to in the literature as overlap syndrome (Flenley, 1985). About 20% of COPD patients have OSA; conversely, COPD—frequently undiagnosed—is thought to exist in about 10% of patients with OSA (Brander, Kuitunen, Salmi, & Partinen, 1992).

Despite the notion that COPD could predispose in some way to the development of OSA (Chaouat et al., 1995; Guilleminault, Cummiskey, & Motta, 1980), evidence of this effect has been scant (Sanders et al., 2003), and it is likely that the coexistence of these two disorders within the same individual has more to do with chance than with any common underlying etiological factor.

The distinction of "overlap" patients (as opposed to patients with "lone" OSA) is a decreased respiratory drive: these patients are more frequently hypoxemic and hypercapnic (Resta et al., 2000) than patients with lone OSA, have higher mean pulmonary artery pressures (Zamarrón, García Paz, Morete, & Matías, 2008), and tend to develop right heart failure earlier (Bradley et al., 1985) than do individuals who have either COPD or OSA alone. Physiological derangements are more likely to be significant when the COPD component is severe (GOLD Stage 3 or 4) (Hiestand & Phillips, 2008). Overlap patients are also more frequently male, older, but not necessarily more obese than patients with "lone" OSA (O'Brien & Whitman, 2005; Zamarrón et al., 2008).

Emphysematous COPD patients ("pink puffers") are frequently underweight (Sanders et al., 2003): since low BMI protects against OSA, this may account for the relatively low prevalence of OSA in COPD patients overall (McNicholas, 2009). Most patients with overlap syndrome are of the "blue bloater" COPD phenotype, which has marked similarities with the obese sleep-apneic individual. Predictably, these patients respond favorably to positive airway pressure therapy.

A potential confounder in this scenario is the effect of smoking. Smoking is a common risk factor for both COPD and OSA. Smokers also tend to have a higher AHI than nonsmokers, and are more likely to manifest OSA than nonsmokers (Wetter, Young, Bidwell, Badr, & Palta, 1994). This led early investigators to imagine that COPD could predispose to the development of OSA. In those COPD patients who develop OSA, it is likely that obesity and smoking (the latter is well known to compromise the small airways, but can also produce inflammation and edema of the upper airway) play a complementary role (Kim et al., 2012). Thus, flow limitation occurs both during expiration (on account of COPD) as well as during inspiration (on account of both OSA and smoking) in these patients (Hiestand & Phillips, 2008).

There is increasing awareness that MS and obesity can heighten the risk of developing asthma (Motala, Pirie, Gouws, Amod, & Omar, 2003): insulin resistance and hypercholesterolemia likely underlie this risk (Cottrell, Neal, Ice, Perez, & Piedimonte, 2011; Fessler et al., 2009). A similar relationship exists between MS and COPD (Ruzena Tkacova, 2010): MS is more likely to be present in COPD patients (Marquis et al., 2005). Such patients have increased levels of circulating inflammatory cytokines from both the lung and adipose tissue (Clini, Crisafulli, Radaeli, & Malerba, 2013), for which reason COPD, like MS, is now positioned as an established risk factor for cardiovascular disease (Engström et al., 2002). Patients with MS appear to suffer more frequent and more severe exacerbations of COPD, and there appeared to be a correlation between fasting glucose and triglycerides levels and number of exacerbations (Küpeli et al., 2010). It follows that when MS, OSA, and COPD coexist within the same individual, the inflammatory response is more intense, though this at present remains speculative.

Unfortunately, studies on the overlap syndrome have been restricted by methodological limitations as well as lack of universally accepted definitions, and this has hindered proper characterization of the prevalence and outcome of this disorder.

CARDIOVASCULAR MORBIDITY

OSA is capable of orchestrating a large spectrum of cardiac and vascular complications. The underlying mechanisms of vascular morbidity principally relate to inflammation, oxidative stress, and sympathetic excitation with resultant endothelial cell dysfunction that occur as a consequence of repetitive arousals (O'Donnell et al., 1999), and chronic intermittent hypoxia. White adipose tissue (WAT) has traditionally been regarded as a storage depot for surplus energy, but has recently been shown to be capable of secreting more than 100 bioactive molecules called adipokines (P Trayhurn & Beattie, 2001). In obesity, the WAT can become functionally dysregulated, driving the development of MS and cardiovascular disease. In obese individuals, the size of a hypertrophied adipocyte often exceeds 200 mm, considerably increasing the distance-to-diffusion of oxygen. Further, as shown by positron emission tomography and xenon washout studies, WAT becomes relatively underperfused in obese individuals, making it vulnerable to hypoxia and inflammation (Trayhurn, Wang, & Wood, 2008). The hypothesis has therefore emerged that adipocyte hypoxia underlies WAT dysfunction, implying a direct causal role for OSA in the genesis and exacerbation of the MS (Lévy, Bonsignore, & Eckel, 2009; Trayhurn et al., 2008). Indeed, OSA has been seen to precede the development of the MS (Agrawal, Sharma, Sreenivas, & Lakshmy, 2011), lending further credence to this theory.

Similarly, tissue hypoxia may also be a player in the progression of non-alcoholic steatohepatitis (NASH) to cirrhosis (Browning & Horton, 2004), compounding the effects of the MS itself, and of age (Dixon, Bhathal, & O'Brien, 2001), on NASH.

HYPERTENSION

In normal subjects during sleep, there is a physiological dip in both in blood pressure and heart rate, without much variability. The acute physiological response to an obstructive apneic episode is biphasic, with a fall in blood pressure followed by a gradual rise. With arousal, an abrupt surge in systolic blood pressure of 20–40 mm Hg can occur (Motta, Guilleminault, Schroeder, & Dement,

1978). The increased sympathetic activity during sleep in OSA patients leads to the development of a nocturnal non-dipping blood pressure profile (O'Brien, Sheridan, & O'Malley, 1988), which ultimately "spills over" into wakefulness (Carlson et al., 1993) and plays an important role in cardiovascular morbidity (Frattola, Parati, Cuspidi, Albini, & Mancia, 1993; O'Donnell et al., 1999; Ryan, Taylor, & McNicholas, 2005; Somers, Dyken, Clary, & Abboud, 1995).

A large body of data implicates the role of OSA in systemic hypertension. In the Framingham study, systolic and diastolic blood pressures related to the number of AHIs, as well as to the duration of hypoxemia during sleep (Nieto et al., 2000). This relationship appears to hold independent of body mass index, waist to hip ratio, and neck circumference. In the Wisconsin Sleep Cohort Study, over a thousand adults (30–60 years of age) were prospectively followed up. Individuals with an AHI of 15/h or more had at least 1.8 times the odds of developing hypertension (Young et al., 1997), which increased to 2.24 when the AHI was >30/h (Haas et al., 2005). The risk appears to be extant at lower AHIs as well (Al-Abri & Al-Hashmi, 2008; Hasan et al., 2012).

CPAP therapy has been shown to reduce sympathetic drive and normalize nocturnal blood pressure in OSA, both in the short term (Dimsdale, Loredo, & Profant, 2000; Somers, Dyken, Clary, & Abboud., 1995) and middle term (Becker et al., 2003), though more long-term studies are required. Daytime somnolence, however mild, seems to be an important predictor of a favorable response to CPAP therapy (Hui et al., 2006; Robinson, Smith, Langford, Davies, & Stradling, 2006). It has been suggested that daytime sleepiness could be a marker for the risk of hypertension in OSA (Kapur, Resnick, Gottlieb, & Sleep Heart Health Study Group, 2008).

Hypertensive patients with MS who have OSA appear to be at considerably higher risk for cardiovascular events than hypertensive individuals who have MS without OSA (Punjabi et al., 2004; Venkateswaran & Shankar, 2007). Indeed, hypertensive subjects with OSA almost invariably manifest MS (Akintunde & Opadijo, 2012).

Should all patients with systemic hypertension, then, be evaluated for OSA? Unfortunately, current literature is ambiguous on this issue. It might be reasonable to evaluate those hypertensive patients with symptoms of excessive daytime sleepiness or fatigue, as well as those patients requiring multiple drugs for hypertension control, or those in whom blood pressure is difficult to control with standard therapy.

ARRHYTHMIAS

Non-rapid eye movement (NREM) sleep appears to have a protective effect against cardiovascular events. The metabolic rate during NREM sleep is low, and malignant ventricular arrhythmias are rare (Andrews et al., 1993; Muller et al., 1987). Since, NREM comprises the major part (75–80%) of total sleep time, nocturnal arrhythmias are overall rare, unless sleep apnea (obstructive or central) is present. Indeed, a clue to the presence of a coexistent sleep apnea may be the onset of a nocturnal ventricular arrhythmia.

Most arrhythmic activity occurs during *rapid eye movement (REM) sleep* (Kales & Kales, 1970). During phasic-REM, apnea-related hypoxemia (Galatius-Jensen et al., 1994) as well as the tachycardia that occurs as a consequence of the increased sympathetic discharge can decrease diastolic coronary perfusion time and trigger nocturnal angina in patients with extant atherosclerotic coronary artery stenosis (King, Zir, Kaltman, & Fox, 1973; Kirby & Verrier, 1989). Overall though, the sympathetic tone in REM sleep falls below that during NREM sleep; as in NREM sleep, parasympathetic discharge increases (Otsuka, Ichimaru, Yanaga, & Sato, 1983).

OSA is associated with the entire spectrum of dysrhythmias, and can in fact be the primary pathology driving arrhythmogenesis. In the Sleep Heart Health Study, OSA patients ran up to a four-fold risk of arrhythmias (Mehra et al., 2006). In patients with OSA, arrhythmias can occur in the absence of conduction system disease (Guilleminault, Connolly, & Winkle, 1983).

Considerable interest is now centered on *cardiac* adiposity as a player in the development of an unfavorable cardiovascular risk profile. The quantity of subepicardial fat (adipose deposits that lie beneath the visceral pericardium) is generally proportionate to overall body adiposity, and the presence of MS in particular (Bertaso, Bertol, Duncan, & Foppa, 2013). When the deposits of subepicardial fat are excessive, strands of fat cells can penetrate into the subjacent myocardium, especially in the vicinity of the right ventricle and right atrium, with possible implications for arrhythmogenesis (Shirani & Roberts, 1993). There is also emerging evidence that subepicardial fat can actually modulate the structure and function of the heart through local paracrine interactions with the contiguous myocardium (Iacobellis & Sharma, 2007).

Patients with MS have an almost 70% greater risk of sudden (and non-sudden) death (Empana, Duciemetiere, Balkau, & Jouven, 2007). Patients with OSA have a very high prevalence of nocturnal sudden cardiac death, and the risk appears to correlate directly with the severity of OSA (Gami, Howard, Olson, & Somers, 2005).

Bradyarrhythmias (comprising sinus bradycardia, various degrees of atrioventricular block, and ventricular asystole) are the most common type of arrhythmia seen in OSA (Simantirakis et al., 2004).

The Diving Reflex

Aquatic mammals and diving birds possess a particular reflex that serves to conserve their oxygen stores. During deep dives, stimulation of their surface receptors with cold water triggers peripheral vasoconstriction, which preferentially diverts blood to the brain and heart. As well, acute vagally mediated bradycardia decreases cardiac oxygen demand. Together, these responses enable marine animals to stay underwater for prolonged periods of time. The reflex is much attenuated in humans but nonetheless, a prolonged apneic spell will result in increased sympathetic output to the peripheral blood vessels causing vasoconstriction; and also increase the cardiovagal tone, slowing down the heart rate (Daly, Angell-James, & Elsner, 1979).

Predictably, most bradyarrhythmic events occur just after, or even during the course of, apneic spells, and predominate during REM sleep (Becker, Brandenburg, Peter, & Von Wichert, 1995; Koehler et al., 2000); their frequency correlates with the severity of the OSA (Guilleminault et al., 1983). In a rather small study, patients with uncomplicated MS were seen to have a greater dispersion of ventricular repolarization time and increased QTc_{min} and QTc_{max} (Soydinc, Davutoglu, & Akcay, 2006).

Because bradyarrhythmias occur predominantly or exclusively at night, they can be difficult to diagnose (Grimm et al., 2000). Individuals with unexplained arrhythmias, or those with nocturnal bradyarrhythmias, should undergo a sleep study (Stegman, Burroughs, & Henthorn, 1996). CPAP therapy will almost invariably prove curative; in fact, arrhythmias may be difficult to abolish in the absence of specific treatment of OSA (Grimm et al., 2000). Atrial overdrive pacing seems to be of uncertain or no benefit in this regard, and pacemaker implantation should be reserved for those patients who fail to respond to CPAP or have an underlying conduction defect (Krahn et al., 2006). On the other hand, there is considerable evidence that CPAP therapy is superior to overdrive pacing (Unterberg et al., 2005). CPAP treatment has also been shown to reduce the frequency of ventricular escape beats that these patients are prone to develop (Ryan, Usui, Floras, & Bradley, 2005).

Atrial fibrillation (AF) is one of the commonest dysrhythmias associated with OSA (Gami et al., 2004) and is liable to occur even in the absence of underlying ischemic heart disease or diastolic heart failure (Fung et al., 2002). Most AF occurs during apnea-related hypoxemic episodes (Roche et al., 2003). As well, the chronic repetitive swings in intrathoracic pressure caused by labored breathing against an occluded airway can increase cardiac wall stress (Schäfer et al., 1998; Tkacova, Rankin, Fitzgerald, Floras, & Bradley, 1998), resulting in atrial remodeling. In one study, among patients suffering from non-valvular paroxysmal AF, patients with MS had a mean atrial size of 46.2 ± 4.3 mm, whereas those without MS had a mean atrial size of 41.6 ± 1.9 mm ($p < 0.011$), underscoring the possible role of atrial wall remodeling in the genesis of atrial fibrillation (Nicolaou et al., 2007).

In the Niigata Preventive Medicine Study (Watanabe et al., 2008), MS was associated with increased risk of AF. Obesity itself has been shown to strongly correlate with the risk of paroxysmal AF after isolated coronary artery bypass grafting surgery in patients older than 50 years (Echahidi et al., 2007), but in younger subjects (in whom this relationship was not demonstrable), it was MS that was the principal risk factor that was independently correlated with paroxysmal AF.

Again, CPAP treatment most often proves therapeutic: in one study, without attention to OSA, the recurrence rates of AF were be seen to twice as high as those in CPAP-treated patients (Kanagala et al., 2003).

Sleep apnea can predispose to *ventricular arrhythmias*, especially against the background of heart failure (Fichter et al., 2002) or acute myocardial infarction (Marin, Carrizo, & Kogan, 1998), or following coronary artery bypass surgery (Echahidi et al., 2007). Episodes occur particularly during episodes of hypoxemia (Shepard, Garrison, Grither, & Dolan, 1985) or hypocapnia (Javaheri & Corbett, 1998). Again, CPAP therapy has been shown to be protective (Javaheri, 2000).

CONUNDRUMS

The relationship between MS, obesity, and sleep apnea is as complex as it is intriguing. Attempts to establish unequivocal links between sleep apnea and MS should take into account the common risk factors for these entities (obesity and age being the chief of these). As Dempsey puts it, "solving the algebraic equation Z–X and extracting the Z component from syndrome X is proving extremely difficult" (Dempsey, Veasey, Morgan, & O'Donnell, 2010).

Obesity, of course, predisposes to OSA; on the other hand, OSA (through the fatigue, sleepiness, and physical inactivity it engenders) promotes obesity. It has been argued that common pleiotropic effects such as hypertension, central obesity, dyslipidemia—as well as sleep apnea—are determined by common genetic factors; syndrome Z may just be an extended form of MS.

Excess fat deposits in the parapharyngeal area doubtless play a part in the genesis of OSA by compromising the airway (Davies & Stradling, 1990). On the other hand, many persons with OSA do not manifest any of the structural

abnormalities of the upper airway that are known to predispose to airway obstruction during sleep (Carmelli, Swan, & Bliwise, 2000). Indeed, there seems to be a stronger relationship between OSA and central obesity than between OSA and parapharyngeal adiposity (Larsson et al., 1984), which suggests mere mechanical loading may not be the only contributory factor involved.

The relationship between OSA and diabetes is unresolved. The Wisconsin study found that OSA subjects ran twice the risk of developing diabetes, and this risk was independent of known confounders, but somewhat confusingly, the increase in the incident risk for diabetes was not perceived to be high after 4 years of follow-up (Reichmuth, Austin, Skatrud, & Young, 2005). Not all authors were able to establish an unequivocal relationship between OSA and glycemic control (Lam et al. 2010). Several studies have demonstrated improvements in glycemic control in the short (Harsch et al. 2004) and long- term (Schahin et al. 2008) with CPAP therapy. On the other hand, other investigators found no evidence that untreated OSA adversely impacts glycemic control (Coughlin, Mawdsley, Mugarza, Wilding, & Calverley, 2007; West, Nicoll, Wallace, Matthews, & Stradling, 2007). As in the case of hypertensive patients, CPAP therapy appears to benefit most those patients who report excessive daytime somnolence (Barceló et al., 2008), raising more questions. It is also possible that at least some of the improvements in glycemic control could have been achieved by lifestyle modification and anti-diabetic medication, and not by CPAP therapy alone. By the same token, it is likely (Dorkova, Petrasova, Molcanyiova, Popovnakova, & Tkacova, 2008; Lam et al., 2010), but not undisputable (Comondore et al. 2009; Robinson, Pepperell, Segal, Davies, & Stradling, 2004), that CPAP has a beneficial effect on lipid metabolism.

As discussed, obesity itself is strongly linked to cardiovascular disease. Unfortunately, most of the earlier studies that addressed the risks of obesity in cardiovascular disease failed to examine the role of OSA (Romero-Corral et al., 2006). Case series and case-control studies that comprise the bulk of the literature on this subject cannot tease out the independent risks of OSA from those of obesity. Most studies differ considerably with regard to the degree of obesity and gender distribution: most authors have typically studied moderate to severe OSA in male subjects.

The vast majority of studies utilize AHI to diagnose and quantify the severity of sleep apnea—unfortunately, to the exclusion of other important variables. For instance, the Respiratory Disturbance Index measures perturbances other than overt apneas and hypopneas—such as periodic limb movements and snore arousals—the sleep disturbances that occur as a consequence of which can impact on metabolic disturbances (Novoa et al., 2011). In addition, most studies have traditionally relied on surrogate indices such as measurements of blood pressure, cardiac function, and serum catecholamine levels rather than more relevant indicators of outcome such as quality of life, functional class, frequency and duration of hospitalization, and mortality. Only a handful of relatively small trials have examined the efficacy of interventions considered the gold standard (such as CPAP) against these outcomes. The possibility of a placebo effect with CPAP confounds issues further. For example, with respect to hypertension, despite data from several randomized, placebo-controlled trials, it is still unclear how much of the improvement in blood pressure can be ascribable to CPAP. The fact that sub-therapeutic CPAP does not improve blood pressure despite cutting the AHI by half (Becker et al., 2003) argues in favor of pathogenetic pathways other than intermittent hypoxia—such as repetitive arousals—that CPAP might also counteract.

Most patients with untreated OSA are at a survival disadvantage. OSA morbidity is especially high in those with excessive daytime somnolence, in males (Punjabi & Polotsky, 2005), and in younger individuals (Lavie, Lavie, & Herer, 2005). It is likely that these individuals benefit the most from early diagnosis and treatment. Why older individuals are relatively protected from the adverse cardiovascular consequences of sleep apnea is unclear, but it is feasible that a certain amount of ischemic preconditioning occurs with advancing age (Lavie & Lavie, 2006). Although obese individuals are at greater risk for cardiovascular disease and congestive heart failure (Kenchaiah et al., 2002), obesity may paradoxically confer a survival advantage in chronic, stable heart failure (Curtis et al., 2005). This advantage appears to taper off when BMI rises to 35 kg/m^2 (Parameswaran, Todd, & Soth, 2006).

The propensity to develop sleep-disordered breathing depends on the complex interaction between multiple compensatory processes that vary substantially between person to person, and also within a given individual. Several phenotypes clearly exist within OSA patients. Genome-wide linkage studies of OSA phenotypes (Palmer et al., 2003) suggest that fully half of the genetic determinants of AHI are independent of obesity (Patel, 2005). Notably, there is a much higher prevalence of OSA in males, and in certain ethnic groups (Africans, East Asians) as compared to Western Caucasians (Ip et al., 2004; Young et al., 1993). Indeed, the relationship between obesity and OSA appears to be influenced by ethnicity. In Asian Indians, sleep apnea of comparable severity has been associated with a relatively low BMI (Udwadia, Doshi, Lonkar, & Singh, 2004). Asian Indians have a relatively high proportion of body fat and a commensurately low muscle mass, which also predisposes them to MS (Misra et al., 2001; Ramachandran, Snehalatha, Satyavani, Sivasankari, & Vijay, 2003).

The critical importance of defining those phenotypes with the highest risk of morbidity underscores the importance of any current research that focuses on the elaboration of candidate genes linking the genetic mechanisms of obesity with sleep apnea.

CONCLUSIONS

Common risk factors and complex associations between sleep apnea and metabolic syndrome have come in the way of understanding the precise determinants of these two entities. Recent advancements in adipose tissue biology and greater awareness of the role of intermittent hypoxia have paved the way for unraveling these complexities. OSA and the MS exhibit a bidirectional relationship, and several disparate clinical patterns fall under their common ambit. Untreated OSA can adversely impact upon each of the individual constituents of the MS, and treatment of OSA with CPAP therapy benefits most of these. Future challenges include not only the clarification of extant ambiguities, but also the integration of CPAP therapy into treatment protocols, along with goal-oriented lifestyle interventions that target specific cardiovascular risks.

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Chapter 17

Circadian Misalignment and Metabolic Consequences: Shiftwork and Altered Meal Times

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OVERVIEW

Virtually all aspects of human physiology (sleep–wake cycles, body temperature, hormone secretion, etc.) are mapped onto 24-h rhythms, and normal coordination of these processes depends on internal clocks. There is a master clock in our brain (located in the suprachiasmatic nucleus, SCN) and peripheral clocks in other organs. The master clock orchestrates periods of feeding/fasting, and peripheral clocks generate 24-h oscillations of energy storage and utilization (Bass, 2012). When properly aligned these clocks optimally regulate metabolism and behavior across the 24-h cycle.

Shiftwork causes circadian misalignment, altering hormonal production and metabolic rhythms (Herichova, 2013). This disruption is associated with an increased risk for obesity, type 2 diabetes, the metabolic syndrome, and gastrointestinal disorders (Froy, 2010; Karlsson, Knutsson, & Lindahl, 2001; Kivimaki, Batty, & Hublin, 2011; Knutsson & Boggild, 2010). An increasing proportion of the population is engaged in shiftwork (Rajaratnam & Arendt, 2001). For example, more than 1.4 million Australians are shiftworkers. Of these, 15% work regular night or evening shifts and 46% work rotating shifts (ABS, 2010). Laboratory studies have demonstrated that shiftwork schedules (Varcoe et al., 2013) and insufficient sleep (Reynolds et al., 2012) result in changes to glucose metabolism. Even a short period of insufficient sleep (two days with either 4 or 10 h sleep opportunity) can result in substantially impaired glucose tolerance (Spiegel, Tasali, Penev, & Van Cauter, 2004). Therefore, the combination of sleep loss and circadian desynchrony renders shiftworkers particularly vulnerable to negative metabolic outcomes.

Metabolic disturbances appear rapidly in response to circadian misalignment. Short-term circadian desynchrony in healthy men and women (Scheer, Hilton, Mantzoros, & Shea, 2009) increases postprandial glucose (a result of inadequate pancreatic insulin secretion (Buxton et al., 2012)), and completely inverts the cortisol profile. The importance of a synchronized circadian system for healthy metabolic function is also evident from studies in mice with a genetic mutation of the clock gene that exhibits a reduced metabolic rate and obesity (Turek et al., 2005), and from genome-wide association studies in humans that have found other clock genes (e.g., *Bmal*1 and *Cry*2) are associated with susceptibility to type 2 diabetes and elevated blood glucose concentration, respectively (Dupuis et al., 2010; Woon et al., 2007). Together, these studies underscore the importance of a synchronized circadian system for healthy metabolic function and how circadian disruption can result in metabolic disease.

Meal timing plays an important role in circadian synchrony; irregular patterns of fasting and feeding can uncouple the

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master and peripheral clocks (Bass, 2012), leading to adverse metabolic outcomes. In humans, night-time eating has been found to shift circadian rhythms in traditional circadian markers such as core body temperature (Krauchi, Cajochen, Werth, & Wirz-Justice, 2002). In addition, when daily energy intake is apportioned such that the majority of calories are ingested late in the day, there is an increased risk of obesity (Baron, Reid, Kern, & Zee, 2011). Moreover, the ability to lose weight is reduced compared to those who consume the same amount of calories earlier in the day (Jakubowicz, Barnea, Wainstein, & Froy, 2013). Even just shifting the consumption of the main meal to after 15:00 results in slower weight loss, and a reduction in total weight lost, compared to those eating earlier in the day (Garaulet et al., 2013). Eating at night is also associated with increased prevalence of digestive complaints, thought to be due to reduced gastrointestinal activity at night (Knutsson & Boggild, 2010; Stenvers, Jonkers, Fliers, Bisschop, & Kalsbeek, 2012).

Shiftwork also changes meal and snack content, although this appears to be highly dependent on the industry type, country and cultural norms, as well as age and gender of the workers (de Assis, Kupek, Nahas, & Bellisle, 2003; Lennernas, Hambraeus, & Akerstedt, 1995; Morikawa et al., 2008; Sudo & Ohtsuka, 2001). Studies have reported that shiftworkers may crave or select foods that are high in fat or sugar (Heath et al., 2012; Persson & Mårtensson, 2006) and may choose foods based on convenience (de Assis et al., 2003). Taken together, research suggests that timing of food intake and food selection may exacerbate altered metabolic function in shiftworkers resulting from changes to their sleep/wake schedule (Figure 1). This chapter will review mechanisms underpinning adverse metabolic outcomes, and examine evidence from human studies relating to the potential implications of irregular food intake.

MISALIGNED CLOCKS AND PHYSIOLOGICAL CONSEQUENCES—MECHANISMS

Central and Peripheral Clocks

All diurnal and nocturnal animals share a common circadian timing system. In mammals, the SCN is the central master clock controlling daily rhythms in behavior

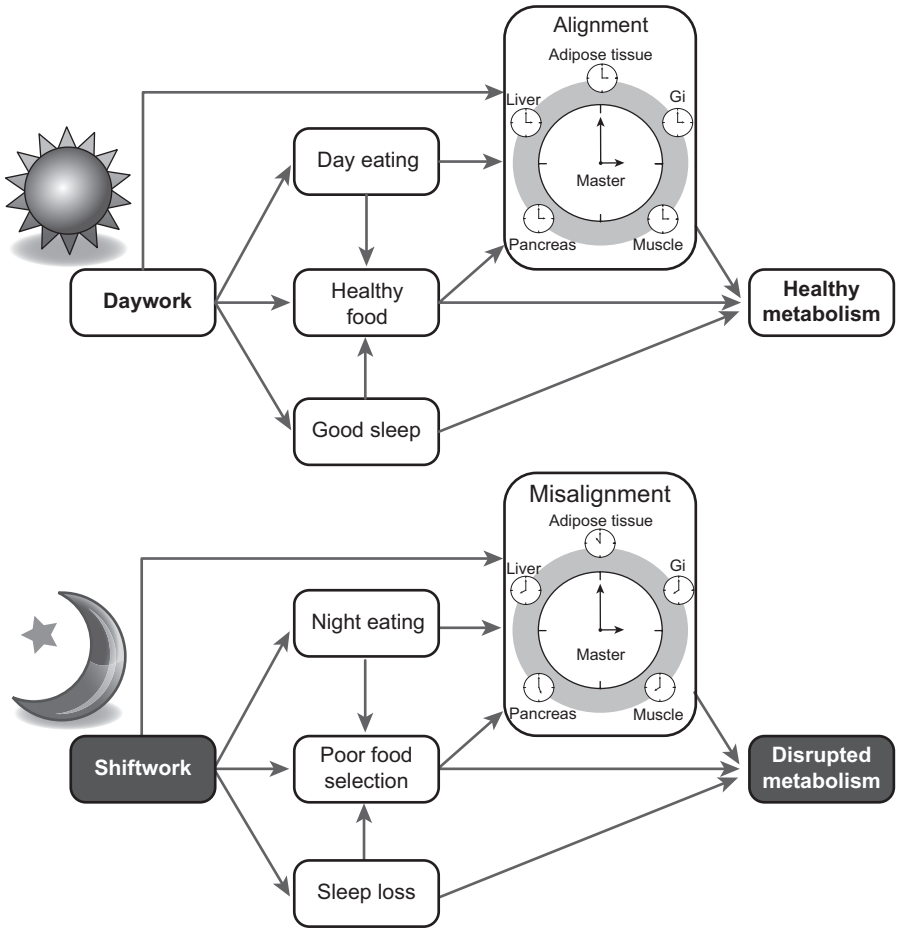

FIGURE 1 Schematic representation of the proposed mechanisms by which shiftwork contributes to disruptions in metabolism, and ultimately poor health outcomes.

(sleep/wake and feeding/fasting) and physiology. Light entrains this central master clock and enables it to subtly change in response to the external light/dark cycle. There are also clocks in peripheral organs (e.g., liver, muscle, pancreas, heart, adipose tissue), which are influenced by systemic cues, the most important being feeding/fasting cycles. Differential sensitivity of clocks across the body to external and internal entraining signals (such as food intake) allows dynamic shifts in some rhythmic processes, whereas others (such as the SCN) remain tied to the prevailing photoperiod (Bechtold & Loudon, 2013). Both the central and peripheral clocks are required for proper metabolic function. Researchers have investigated clock systems down to the cellular level, and a number of genes have been implicated in the regulation of circadian timing. There are several recent reviews in this area—the reader is directed to Buhr and Takahashi (2013), Cagampang and Bruce (2012), Li, Li, and Wang (2012).

The physiological consequences of misaligned clocks are wide-ranging, with tissue-specific effects. The proposed gastrointestinal (GI) and metabolic mechanisms for these effects are illustrated in Figure 2. At the top of this figure, the clock misalignment, as would typically be experienced by shiftworkers, is represented. Light information enters through the optic nerve and is received by the master clock in the SCN. The central clock signals the peripheral clocks via indirect and direct mechanisms, resulting in metabolic dysfunction.

Although the SCN serves as the master synchronizer of the entire system, food intake at irregular times can uncouple peripheral clocks from the SCN (Damiola et al., 2000). In rodents given access to food for only a few hours during their usual rest period, peripheral clocks phase shift by as much as 12 h within a week (Damiola et al., 2000; Stokkan, Yamazaki, Tei, Sakaki, & Menaker, 2001). The clock system in the liver entrains particularly rapidly to food availability, with large phase shifts occurring within 2 days of an altered feeding schedule (Stokkan et al., 2001). The SCN however, does not respond to the feeding signals, and it can take people several weeks to physiologically adapt to jetlag when traveling across many time zones. In the case of shiftworkers, they may never adapt to their work schedules, even when working many nights in a row (Ferguson, Kennaway, Baker, Lamond, & Dawson, 2012).

While strong evidence already supports that timed meals can alter the circadian rhythms of animals, evidence in humans is currently limited to one study (Krauchi et al., 2002). Healthy young males ate a single carbohydrate-rich meal either in the morning (08:30–09:00) or evening

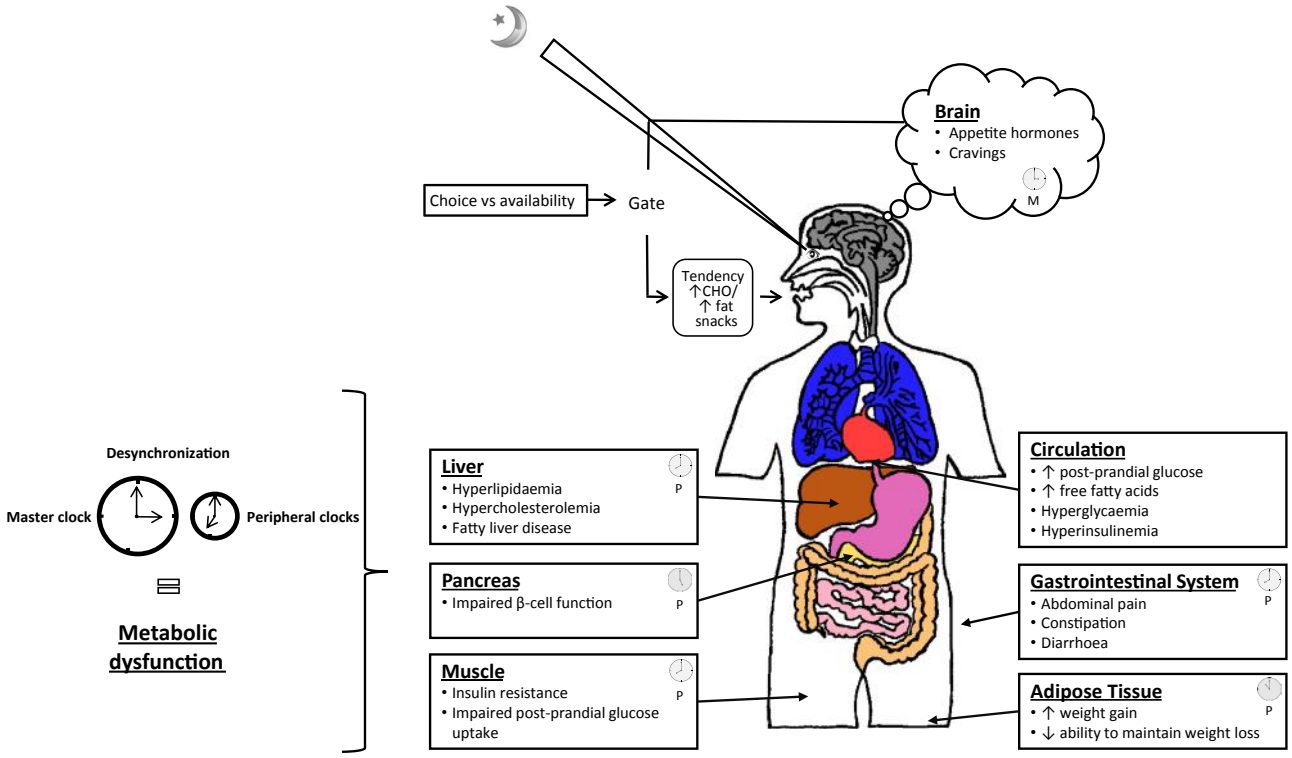

FIGURE 2 Eating during normal rest periods is a main factor contributing to this desynchronization of master and peripheral clocks in shiftworkers. This leads to metabolic dysfunction. At night, possible changes in appetite hormones, cravings, food choice and availability affect food consumption. The physiological consequences of metabolic dysfunction in the liver, pancreas, muscle tissue, circulation, GI system, and adipose tissue are shown. P = peripheral clock, M = master clock.

(21:30–22:00) for 3 days while maintaining their regular sleep times (24:00–07:30). Under these normal sleep/wake conditions, the periodic meals advanced the body temperature rhythm by 1 h and the heart rate rhythm by 45 min, but did not change the timing of the salivary melatonin rhythm. Consistent with animal data, this study suggests that feeding/fasting can be an internal time cue in humans, dissociating peripheral clock outputs (core body temperature and heart rate) from the central clock (melatonin).

Shiftworkers, Food Intake, and Circadian Misalignment

Shiftworkers often eat at irregular times of day, and research suggests they may select foods that are higher in salt, sugar, and saturated fat (de Assis et al., 2003; Di Lorenzo et al., 2003; Heath et al., 2012). These dietary alterations appear to vary considerably with industry, country, age, and gender of the workers. In one study of Japanese male factory workers, night shiftworkers consumed a greater amount of food during the night compared with day workers (Morikawa et al., 2008), while a study of Japanese female night shift factory workers found overall energy intake was reduced at night (Sudo & Ohtsuka, 2001). Another study in male industrial workers in Sweden also reported lower caloric intake during night shift (Lennernas et al., 1995), while Brazilian garbage collectors report eating larger amounts of food at night compared with day workers (de Assis et al., 2003). Both the Japanese studies and the Brazilian study found poorer diet quality in night shiftworkers, but this was not the case in the Swedish study. The Swedish study reported that macronutrient profile differed in night workers only on their days off, with less carbohydrates and less coffee consumed on the rest days (Lennernas et al., 1995). In considering data from cross-sectional studies, it is important to remember that a number of factors influence food intake, such as age, energy expenditure, food availability, income to spend on food, etc. It would therefore be preferable to compare the same individuals across multiple shifts rather than separate groups on different shifts to gain a clearer understanding of the impact of shiftwork on food intake.

In humans, eating a large amount of food in the night has a number of negative consequences (Morgan, Shi, Hampton, & Frost, 2012). Decreased glucose and lipid tolerance has been reported in shiftworkers in field (Lund, Arendt, Hampton, English, & Morgan, 2001) and in laboratory shiftwork simulation studies (Al-Naimi, Hampton, Richard, Tzung, & Morgan, 2004; Ribeiro, Hampton, Morgan, Deacon, & Arendt, 1998). Late or night shiftworkers have also been found to eat their last daily meal later at night (22:27 vs 17:52), eat fewer meals but consume more calories, and gain more weight since they started their job (4.3 kgs vs 0.9 kgs) than their day shift counterparts (Geliebter, Gluck, Tanowitz, Aronoff, & Zammit, 2000).

Eating late in the day can also reduce the effectiveness of weight-loss programs (Garaulet et al., 2013; Jakubowicz et al., 2013). People following a 20-week weight-loss program lost less weight if the majority of their energy intake occurred late in the day, compared to those that consumed their meal earlier. There were no differences between energy intake, dietary composition, estimated energy expenditure, appetite hormones, and sleep duration between the groups (Garaulet et al., 2013).

Changes in food patterns at night may also be due to cravings for these types of food. Alternatively, reduced availability of food resulting from eating at atypical times of day may drive choice based on convenience (de Assis et al., 2003). Many shiftworkers eat at night, they tend to snack frequently, and consume high-carbohydrate/high-fat foods to keep energy high and alleviate boredom. High sugar beverage intake has also been shown to be high during night shift (de Assis et al., 2003), with other studies reporting that food intake may be driven more by habit and less by appetite in night workers (Waterhouse, Buckley, Edwards, & Reilly, 2003).

The change in macronutrient composition of meals also appears to impact circadian rhythmicity (Stimson et al., 2014). High fat feeding can cause some circadian rhythms, driven by peripheral oscillators, to desynchronize from the rhythms controlled by the SCN (Mendoza, Pevet, & Challet, 2008). High fat diets are able to alter peripheral clock genes with adaptations occurring rapidly following a high fat meal (Pendergast et al., 2013). When high fat diets are restricted and timed appropriately, the detrimental metabolic effects of the high fat diet can be rescued (Hatori et al., 2012; Sherman et al., 2012). In a rodent model, compared with ad libitum feeding, restricting feeding of a high fat diet for 4 (Sherman et al., 2012) or 8 h (Hatori et al., 2012) resulted in reduced overall energy consumption and body weight, improved insulin sensitivity, and increased fat oxidation. Taken together, the data suggest that timing of food intake, macronutrient composition of meals, and food choice are important factors in metabolic regulation.

Organ-Specific Consequences of Misalignment

Shiftworkers eating at night may therefore experience physiological consequences in a number of organ systems. Each organ is discussed in the following points:

GI system—There is evidence that altering normal circadian patterns affects the brain–gut axis, contributing to the pathogenesis of a number of GI and liver diseases (Hoogerwerf, 2009). Core functions of the GI tract (including motility, maintenance and replacement of the protective barrier, and production of digestive enzymes) are altered by circadian oscillations. Changes in the circadian rhythm due to shiftwork or transmeridian flights have been associated with increased prevalence of GI symptoms such

as abdominal pain, constipation, and diarrhea (Konturek, Brzozowski, & Konturek, 2011).

Liver—The circadian clock is also thought to be important for regulation of fatty acid and carbohydrate metabolism in the liver. Mice with disrupted circadian rhythms (clock gene deficient mice) have altered metabolic function and develop metabolic syndrome, hyperlipidemia, hyperglycemia, and fatty liver disease (Turek et al., 2005). The clock genes are strongly regulated by light exposure, and when animals are kept in constant light conditions, peripheral clock genes in both the GI tract and liver alter their circadian oscillating patterns, resulting in disruptions to food intake and behavior. These disruptions are organ-dependent (Polidarova, Sladek, Sotak, Pacha, & Sumova, 2011). For example, selective knockout of *Bmal*1 in the liver causes hypoglycemia, yet the liver remains insulin sensitive (Lamia, Storch, & Weitz, 2008). Different effects are seen in pancreatic- (Marcheva et al., 2010), muscle- (Dyar et al., 2014), and adipose tissue-specific (Paschos et al., 2012) knockouts as described below.

Pancreas—The pancreas is also under circadian regulation, especially insulin production (from β-cells) and the release of pancreatic enzymes amylase and trypsin (Keller, Groger, Cherian, Gunther, & Layer, 2001). Mice deficient in an essential clock gene (*Bmal*1) in the pancreas have severe glucose intolerance and complications with insulin production (Marcheva et al., 2010). Cross-sectional studies of shiftworkers have observed increased β–cell activity compared to day workers (Esquirol, Bongard, Ferrieres, Verdier, & Perret, 2012). In the circulation, glycemic response to meals is altered at different times of the day, with larger blood glucose responses seen at night (Al-Naimi et al., 2004), and sleep restriction combined with this leads to greater impairment of insulin secretion (Buxton et al., 2012).

Muscle—The maintenance of skeletal muscle function is under circadian regulation of a number of genes involved in fatty acid metabolism (Li et al., 2012). Skeletal muscles of genetically altered mice (deficient globally in *Bmal*1), have lower strength and exhibit numerous disruptions to expression of genes required for muscle structure and function (Lefta, Wolff, & Esser, 2011). Skeletal muscle is a major organ for glucose disposal. The muscle-specific *Bmal*1 knockout mouse model has recently been found to have impaired glucose metabolism (Dyar et al., 2014).

Adipose tissue—A number of genes expressed in adipose tissue exhibit circadian patterns, including clock and adipokine genes (such as resistin, adiponectin, and visfatin), which are important in metabolic regulation (Ando et al., 2005). In a global clock gene deficient mouse model, increased fat accumulation in white adipose tissue is seen (Shostak, Meyer-Kovac, & Oster, 2013). Adipose tissue-specific *Bmal*1 knockout mice become obese and show a shift in the diurnal rhythm of food intake without a change in total caloric consumption (Paschos et al., 2012). These mice also have lower levels of lipolysis (the mechanism that allows the release of energy stored in adipocytes) and in return lower levels of fatty acids in circulation. The changes were associated with corresponding changes in the expression of neurotransmitters responsible for appetite regulation in the brain (Paschos et al., 2012). A key hormone involved in signaling information about adipose energy stores to the central nervous system is leptin. Leptin is important in suppressing appetite and is secreted in a circadian pattern, so that normally it is high at night (primed for fasting) and low during the day (primed for food consumption) (Lecoultre, Ravussin, & Redman, 2011). Clock deficient mice have elevated levels of circulating leptin, and are leptin resistant (Turek et al., 2005). Circadian misalignment in humans is associated with lower leptin levels at night (Scheer et al., 2009). A similar response has also been seen when young, healthy students were shifted to a nocturnal lifestyle (by skipping breakfast and consuming the bulk of calories, >50% of their daily food intake in the evening), and limiting sleep to 7 h (between 01:30 and 08:30). After 3 weeks of this regime not only were nocturnal leptin levels lower but also students had impaired insulin responses to glucose (Qin et al., 2003).

The bulk of the specific organ or system studies discussed have been conducted in animal models (Birky & Bray, 2014). Studies in humans have examined the effects of eating at different times of day on metabolic efficiency. These are reviewed in the following section.

MISALIGNED CLOCKS AND PHYSIOLOGICAL CONSEQUENCES—EVIDENCE

To date, a relatively strong argument linking eating at night to differential phase shifting of peripheral clocks and subsequent metabolic dysfunction has been made using primarily animal models. There have been a paucity of studies in humans, and these have varied widely in terms of methodology. Table 1 summarizes findings from nine studies, which include 10 experimental conditions, designed to investigate the metabolic consequences of circadian misalignment as would typically be experienced by shiftworkers. The laboratory studies varied greatly. Of the nine, six were conducted in the laboratory with healthy, non-shiftworking participants (Al-Naimi et al., 2004; Buxton et al., 2012;Gonnissen et al., 2012; Hampton et al., 1996; Ribeiro et al., 1998; Scheer et al., 2009). Wehrens, Hampton, Finn, and Skene (2010) conducted a laboratory study including experienced shiftworkers, and Lund et al. (2001) and Knutsson et al. (2002) conducted observational field studies in shiftwork environments. While some of these studies investigated the effects of phase advances, or shortening the "day length" (Gonnissen et al., 2012; Hampton et al., 1996; Ribeiro et al., 1998), others examined phase delays, or

TABLE 1 Response to Controlled Food Consumption during Shiftwork (Simulated Laboratory Studies and Field Investigations)

First Author/ Year	Participants	Diet	Timing of Meals	Method of Circadian Misalignment	Response to Food during Shiftwork		
					Glucose	Insulin	Lipid- TAG
Simulated Shiftwork: Lab Studies with Non-Shiftworking Participants							
Hampton et al. (1996)	$n=9$, 6 male Healthy, 19–27 years, 45–85 kg	• *High* fat pre-meal • Test meal—3331 kJ (796 kcal): Fat (37%); CHO (52%); Pro (11%)	Test meal at 13:30 clock time. During phase shift this equated to 22:30 body clock time	9 h phase advance	↑	↑	↓
Ribeiro et al. (1998)	$n=12$, 4 male Healthy 19-27 years, BMI = 20–29 kg/m^2	• *Low* fat, high CHO pre-meal • Test meal—3330 kJ (796 kcal): Fat (37%); CHO (52%); Pro (11%)	Test meal at 13:30 clock time. During phase shift this equated to 22:30 body clock time	9 h phase advance	↔	↔	↑
Al-Naimi et al. (2004)	$n=8$, all male healthy, 20–33 years, BMI = 20–25 kg/m^2	• Meals—3138 kJ (750 kcal) to 3180 kJ (760 kcal): Fat (34–38%); CHO (51–55%); Pro (11%) • Snacks—017 kJ (243 kcal): Fat (47%); CHO (48%); Pro (5%)	Pre meal 07:00/19:00, pre snack 10:00/22:00, meal 1 13:00/01:00, snack 16:00/04:00 & meal 2 19:00/07:00	Simulated night versus simulated day shift (crossover)	↑	↑↓	↑
Scheer et al. (2009)	$n=10$, 5 male Healthy, 19–41 years, BMI = 20–28 kg/m^2	• Meals: Fat (25%); CHO (50%); Pro (25%)	Meals relative to wake time—breakfast 1 h, lunch 5 h, dinner 11.5 h & snack 15.5 h	7 × 28 h day length	↑	↑	
Buxton et al. (2012)	11 young, (mean, 23 ± 2 years; 5 male), 10 older (mean, 60 ± 5 years; 5 male)	• Meals: Fat (15–30%); CHO (55–60%); Pro (15–20%) • Identical breakfast, other meals adjusted for weight change ±1 kg	Aligned to baseline breakfast timing	21 × 28 h day length *Plus* sleep restriction to 5.6/24 h	↑	↓	

Gonnissen et al. (2012)	$n=13$, 7 male	• Total energy- 20% breakfast, 40% lunch & 40% dinner. • Composition: Fat (33%); CHO (55%); Pro (12%)	Meals given at regular time points related to cycle duration, exact timing unclear	3 × 21 h day phase advance (7 h sleep) (crossover)	↔	↑	
				3 × 27 h phase delay (9 h sleep)	↑	↔	
Simulated Shiftwork: Lab Studies with Shiftworking Participants							
Wehrens et al. (2010)	$n=24$, all male, 11 shiftworkers (>5 years experience) vs non shiftworkers, 35 ± 7.2 years	• Breakfast- 4050 kJ (968 kcal): Fat (40%); CHO (54%); Pro (8%) • Lunch- 4171 kJ (997 kcal): Fat (54%); CHO (32%); Pro (14%) • Dinner- 3975 kJ (950 kcal): Fat (44%); CHO (43%); Pro (13%)	Breakfast 08:45, lunch 12:45, dinner19:00 & evening snack 22:00	Simulated "first" night shift	↔	↑	↓
Shiftworking Operations with Shiftworking Participants							
Lund et al. (2001)	$n=12$, 10 males, rotating shiftworkers in Antarctica, 24–34 years, 60–88 kg	• Pre meal- 2066 kJ (494 kcal) • Test meal- 3330 kJ (796 kcal): Fat (37%); CHO (52%); Pro (11%)	Pre-meal 08:00 (D9 20:30). Test meal 13:30 (D9–01:30)	7 days 09:00–17:00 Transition to 7 days night 00:00–08:00 Transition back to 09:00–17:00	↑	↑	↑
Knutsson et al. (2002)	$n=11$, all female, nurses, >3 years night work	Test meal- 1860 kJ (445 kcal): Fat (33%); CHO (51%); Pro (16%)	Test meals D12–19:30, 23:30, D13–03:30, 19:30, 23:30 & D14–03:30	Compared days off with meals on night shift	↔	↑	↔

Pre-meal = meals given prior to test meals; Test-meal = meals with post-prandial testing; BMI = body mass index; CHO = carbohydrate, Pro = Protein; TAG = triglycerides; ↑ = significant increase; ↓ = significant decrease; ↑↓ = significant increases and decreases to multiple meals within the same study; ↔ = no significant changes ($p<0.05$).

employed protocols that resulted in lengthening each "day" (Al-Naimi et al., 2004; Buxton et al., 2012; Scheer et al., 2009). Meal composition (i.e., macronutrient distribution) and timing varied across studies; some studies pre-loaded participants before test meals with meals that were high in fat (Hampton et al., 1996) or high carbohydrate (Ribeiro et al., 1998). The field studies were conducted in night workers in a survey station in Antarctica (Lund et al., 2001) and nurses in Sweden (Knutsson et al., 2002). Given the variation in participants, interventions, and environments, it is not surprising that solid conclusions are difficult. While the studies measured a number of different metabolic outcomes, glucose, insulin, and triglycerides (TAG) were most consistently studied across the different methodologies, and are included in Table 1 for comparison:

- *Blood glucose*—increased in the majority of conditions (increased = 6, no significant change = 4).
- *Insulin*—increased in majority of conditions, but with more variable results than for glucose (increased = 7, decreased = 2, no significant change = 2).
- *TAG*—only measured in six of the studies included and varied (increased = 3, decreased = 2, no significant change = 1).

SUMMARY

Overall, results suggest that shiftwork is likely to affect the way in which the body responds to meals, generating elevated glucose and insulin levels and variable responses in circulating TAG. When considered in the context of previous research, timing and composition of meals may play an important role in this relationship. Humans are complex, and given the multi-factorial connections between shiftwork schedules, light, sleep, food timing, and selection, research aimed at teasing out the relative contributions, and interactions, between these variables would be highly beneficial. If eating at night exacerbates circadian desynchrony and contributes to health risk in shiftworkers, interventions based on reducing calorie consumption at night may be a valuable avenue for investigation to prevent metabolic disease.

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Chapter 18

Role of Sympathetic Nervous System in the Metabolic Syndrome and Sleep Apnea

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INTRODUCTION

In the past decades, clinicians and investigators have clearly shown, through experimental and clinical studies, the role of the sympathetic nervous system in the pathophysiology of several cardiovascular and noncardiovascular conditions. This review will be aimed at focusing and discussing the new information collected on two particular conditions, such as metabolic syndrome and sleep apnea. The first one is a clustering condition with several "actors" and relative pathophysiological mechanisms. It is well known that some of these "actors" are also present in the sleep apnea syndrome. After a brief introduction on the different "actors" involved, the article will address several other issues: (1) the sympathetic overdrive in metabolic syndrome, (2) the hyperadrenergic tone in sleep apnea syndrome, (3) mechanisms responsible for the sympathetic abnormalities, and (4) sympathetic activation and cardiovascular risk. The final part will be focused on the therapeutic implications for the control of the hyperadrenergic state and the clinical related conditions.

THE METABOLIC SYNDROME: THE "ACTORS"

Because of epidemiological evidence, the increase in cardiovascular morbidity and mortality, and the great impact on public health, there was, in the past decades, an increasing interest in a condition characterized by various combinations of abnormalities in body weight, glucose metabolism, lipid metabolism, and blood pressure. Several definitions were used to characterize it (Kaplan, 1989; Reaven, 1988), but it is now universally referred to as "metabolic syndrome," a definition proposed by the US National Cholesterol Education Program Adult Treatment Panel III (ATP III) (NCEP-ATP III, 2001). It requires the presence of at least three of the following five factors for diagnosis: waist circumference greater than 102 cm in men and 88 cm in women, elevated plasma triglyceride levels (≥150 mg/dL), reduced high-density lipoprotein (HDL) cholesterol (<40 mg/dL in men and <50 mg/dL in women), elevated fasting glucose (≥110 mg/dL), and blood pressure in the high-normal (≥130 mmHg systolic or ≥85 mmHg diastolic) or hypertensive range.

The application of this definition allows us to observe in the population that the metabolic syndrome is so widespread because it affects approximately one of five individuals, is common in both sexes and all ethnic groups, with a high prevalence being observed in both developed and developing countries from all continents, and the peak of prevalence is in middle-aged and elderly individuals (Lorenzo et al., 2006; Park et al., 2003).

The definition of metabolic syndrome is under revision after several modifications advanced: (1) to lower the cutoff blood glucose value to 100 mg/dL or greater; (2) to consider a waist circumference greater than 94 cm in men and 80 cm in women associated with two other criteria selected from an elevated fasting glucose (≥100 mg/dL), a low HDL

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cholesterol level, an elevated triglyceride level, and a high-normal blood pressure; and (3) to include detailed lipoprotein abnormalities and proinflammatory or prothrombotic factors, given the link with atherosclerosis and excessive adipose tissue mass (Alberti, Zimmet, & Shaw, 2005; Malik et al., 2005).

Arguments of the debate are the limitations of the concept of "syndrome," because: (1) frequently there is no standardization and uniformity between different laboratories in the determination of the different variables mentioned in the definition, and (2) there is no unifying pathophysiological background for the disease definition. The previously mentioned limitations are strengthened by the evidence reported by two studies, that for both coronary artery disease and the overall cardiovascular risk profile the prognostic information associated with the syndrome is not greater than the sum of its parts (Iribarren et al., 2006; Mancia et al., 2007). At present, the ATP III definition is the preferred choice, even when the definition recently proposed by the International Diabetes Federation (Alberti et al., 2005) is taken into account.

Several mechanisms are postulated as the major determinants of the syndrome. These include genetic factors, insulin resistance, atherogenic dyslipidemia, visceral obesity, and chronic low-grade inflammation (Esposito & Giugliano, 2004; Ritchie & Connell, 2007; Siani & Strazzullo, 2006). It is likely that the previously described factors may interact with each other, making the pathophysiologcal picture difficult to be separately analyzed (Iribarren et al., 2006). The hypothesis is that all the previously mentioned mechanisms have a common pathogenetic background in the sympathetic nervous system activation. Several lines of evidence have been provided that sympathetic neural influences are involved in the regulation of energy expenditure, by modulating basal metabolic rate and facilitating the thermogenic response to food intake (Reaven, Lithell, & Landsberg, 1996), and in homeostatic control of blood pressure values (Landsberg, 1986). This has led to the hypothesis that the sympathetic nervous system represents the common underlying pathogenetic link among the various components of the metabolic syndrome. The single components will be reviewed thereafter.

HYPERTENSION

Several lines of evidence provide univocal support of the hypothesis that high blood pressure state is characterized by sympathetic overactivity. Data collected in young patients with borderline hypertension and hyperkinetic circulation display a resting tachycardia associated with increased plasma norepinephrine values (Julius et al., 1991). It has been clearly shown that heart rate values depend on both vagal and sympathetic neural influences (Grassi & Mancia, 2003) and correlate with other independent markers of adrenergic drive (Grassi, Vailati, et al., 1998). Thus, the conclusion can be drawn that early hypertensive phases are already characterized by a hyperadrenergic state. More recently, both indirect and direct measures of sympathetic function have definitively confirmed this hypothesis. A meta-analysis of the studies on the basis of plasma norepinephrine as a marker of adrenergic function has shown that circulating levels of this substance are greater in hypertensive than in age-matched normotensive patients (Goldstein, 1983). In more recent years, techniques based on direct assessment of sympathetic tone (e.g., the microneurographic recording of efferent sympathetic nerve traffic to the skeletal muscle district) and the assessment of the spillover rate of norepinephrine into the systemic circulation, via the so-called norepinephrine radiolabeled technique, have documented an increased central adrenergic outflow and an increased release of the adrenergic neurotransmitter from nerve terminals in hypertension. This has expanded the information available on the behavior of the sympathetic function in early hypertensive phases to the stable and more severe forms of this pathophysiological condition (Esler, Lambert, & Jennings, 1989; Mancia, Cattaneo, Seravalle, Lanfranchi, & Mancia, 1998). Figure 1 refers to the results of a microneurographic study performed in mild and more severe essential hypertensive patients (Mancia et al., 1998). Indeed, when the nerve firing rate was assessed in normotensive middle-aged subjects and in untreated age-matched patients displaying blood pressure elevations of increasing severity, the results showed that mild and more severe essential hypertension was characterized by sympathetic overactivity. Thus, the degree of adrenergic activation is directly proportional to the severity of the hypertensive state.

Three other findings deserve to be mentioned. First, the sympathetic overactivity appears to be a specific feature of the essential hypertensive state, because no adrenergic overdrive is reported in secondary forms of hypertension, such as in renovascular hypertension or in hyperaldosteronism. Second, an increased sympathetic nerve-firing rate is also evident in elderly subjects with isolated systolic or systodiazstolic hypertension (Grassi, Seravelle, Bertinieri, et al., 2000). Third, adrenergic overdrive contributes to the development and progression of the target organ damage, particularly at the cardiac and vascular levels (Greenwood, Scott, Stoker, & Mary, 2001; Mancia, Grassi, Giannattasio, & Seravalle, 1999; Schlaich et al., 2003). The norepinephrine spillover technique has demonstrated that there is an increased secretion of norepinephrine from sympathetic nerve terminals in hypertension and that this increase occurs in organs displaying a specific prohypertensive pathogenic role, such as kidney, or in districts exposed to complications of the hypertensive state, such as the cerebral and the coronary circulation (Esler et al., 1989; Ferrier et al., 1992). A further peculiar feature of the neurogenic dysfunction is represented by the evidence that the central sympathetic overdrive is associated

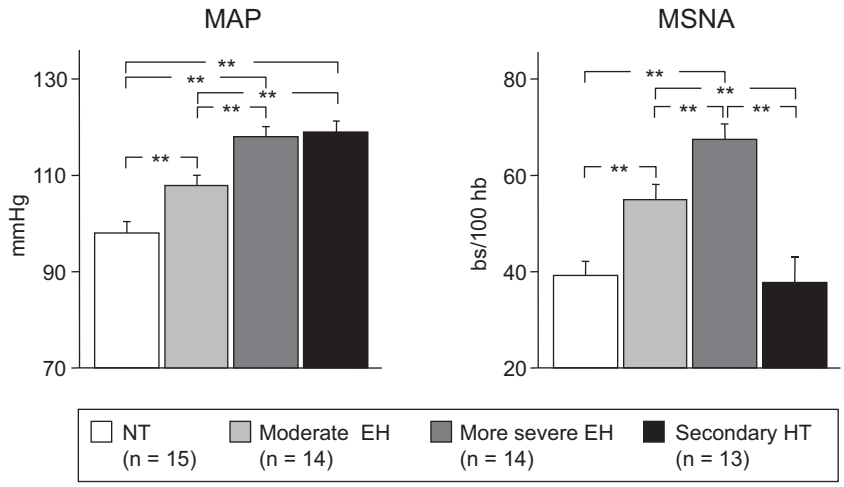

FIGURE 1 Mean (±SEM) values of mean arterial pressure (MAP) and muscle sympathetic nerve activity (MSNA) in normotensive subjects (NTs), moderate essential hypertensives (moderate EHs), more severe essential hypertensives (more severe EHs), and secondary hypertensives (secondary HTs). $^{**}P<0.01$. *Modified from (Mancia et al., 1998).*

at the peripheral vascular level with a down-regulation of β-adrenoreceptors (Grassi & Mancia, 2004) that are physiologically involved in facilitating the thermogenic responses to food (Silva, 2006). The dysfunction of these receptors may explain why hypertensive patients may be more prone to overweight or obesity. Although the mechanisms responsible for the adrenergic overdrive of the hypertensive state are complex, it is likely that reflex, metabolic, and humoral factors play a role. These factors include a dysfunction in cardiopulmonary receptor modulation of adrenergic drive and a state of insulin resistance or the renin-angiotensin-aldosterone activation. These two latter factors are greatly involved given the evidence that insulin and angiotensin II exert pronounced sympathoexcitatory effects (Esler et al., 2006; Frontoni, Bracaglia, & Gigli, 2005; Grassi, 2001).

OBESITY

Unlike in hypertension, in obesity the interest of investigators has only recently focused on the behavior of sympathetic function. However, a wide range of information has already been obtained. The obese state, even when unaccompanied by a blood pressure elevation, displays signs of adrenergic activation, such as increased resting heart rate and elevated plasma norepinephrine values (Young & Macdonald, 1992). This has been confirmed by evidence that plasma norepinephrine values are increased in subjects with a body mass index >30 kg/m^2 (Troisi et al., 1991; Young & Macdonald, 1992) and that the augmented circulating levels of the adrenergic neurotransmitter are dependent on a true increase in the sympathetic nerve firing (Grassi et al., 1995; Grassi, Seravalle, Del'Oro, et al., 2000). These findings provide conclusive evidence that the sympathetic overdrive plays a role in human obesity, although the magnitude of this role differs somewhat according to the specific patterns of fat distribution. Figure 2 displays the results of a microneurographic study in which the muscle sympathetic neural drive was assessed in abdominal and in peripheral obesity (Grassi et al., 2004). The degree of sympathetic activation (and the magnitude of the insulin resistance state) is much greater in patients with visceral body fat deposits than in those with peripheral distribution of the adipose tissue. This finding has been further confirmed by the results of a study showing that subcutaneous body fat distribution is not linked to an adrenergic overdrive (Alvarez, Ballard, Beske, & Davy, 2004).

As previously mentioned with regard to hypertension, the mechanisms underlying the hyperadrenergic drive in obese individuals include both reflex and non-reflex factors, such as the condition of insulin resistance, the increase in plasma leptin levels, and the chemoreflex stimulation in the sleep apnea syndrome (triggered by the hypoxic episodes) (Esler et al., 2006; Grassi, 2001; Grassi et al., 1995; Grassi, Facchini, et al., 2005).

SYMPATHETIC ACTIVATION IN THE METABOLIC SYNDROME

The information provided by the single components of the disease suggests that in metabolic syndrome, sympathetic drive to the heart and peripheral circulation may be markedly potentiated. Data collected on this issue in recent years provide evidence that sympathetic activation does occur in the metabolic syndrome. Data based on urinary normetanephrine assay have demonstrated an increase in 24-h excretion of this adrenergic metabolite in patients with the metabolic syndrome (Brunner et al., 2002). In patients with metabolic syndrome, a reduced low-frequency/high-frequency power has also been reported, suggestive of a hyperadrenergic tone (Brunner et al., 2002). A potentiation in systemic norepinephrine spillover has been described in patients with metabolic syndrome (Esler et al., 2006). Finally, two microneurographic studies have shown that middle-aged subjects with metabolic syndrome display greater levels

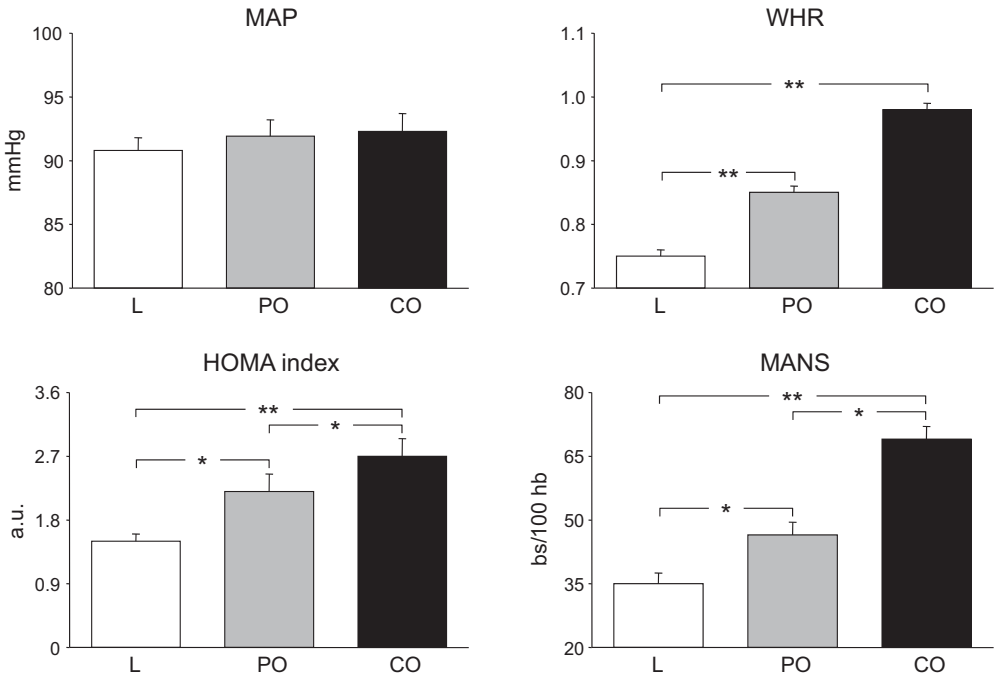

FIGURE 2 Mean arterial pressure (MAP), waist-to-hip ratio (WHR), homeostatic model assessment (HOMA index), and muscle sympathetic nerve activity (MSNA) values in lean subjects (L) and in patients with peripheral (PO) and central (CO) fat distribution. Data are shown as the means (±SEM). $*P<0.05$, $**P<0.01$. *Modified from Grassi et al. (2004).*

of sympathetic nerve traffic (Grassi, Dell'Oro, et al., 2005; Huggett, Burns, Makintosh, & Mary, 2004). Other evidence shows that the sympathetic overdrive does the following: (1) it appears to be independent of the presence of hypertension, because it is detectable even in patients without high blood pressure; (2) it characterizes another condition frequently detectable in the metabolic syndrome (i.e., the hyperglycemic state or the diabetic condition, particularly when associated with hypertension) (Huggett et al., 2003); and (3) it appears to be detectable in cardiovascular diseases that are frequently characterized by sympathetic activation, such as in heart failure complicated by metabolic syndrome (Arenare et al., 2006).

Taken together, these findings provide univocal support for the notion that adrenergic drive is markedly potentiated in the metabolic syndrome and that almost all districts of the cardiovascular system participate in the phenomenon. This potentiation carries adverse prognostic significance, given the evidence that it further aggravates the already elevated cardiovascular and metabolic risk profile of the single components.

THE HYPERADRENERGIC TONE IN SLEEP APNEA SYNDROME

Obstructive sleep apnea (OSA) is a common clinical condition characterized by an exaggerated negative intrathoracic pressure. The combination of increased left ventricular (LV) afterload and diminished LV preload during obstructive apneas causes a progressive reduction in stroke volume and cardiac output. OSA-induced hypoxia might also directly impair cardiac function (Bradley & Floras, 2009; Kasai, Floras, & Bradley, 2012; Somers et al., 2008). Autonomic cardiovascular dysregulation, characterized by elevated sympathetic nerve activity (SNA) and parasympathetic withdrawal, is another hallmark of OSA. All of apnea-induced intermittent hypoxia and CO_2 retention, the absence of breathing during apnea, baroreceptor reflex stimulated by reductions in stroke volume and cardiac output, and arousal from sleep at apnea termination also augment SNA. More importantly, the adverse effects of OSA on the autonomic nervous system are not confined to sleep but may persist into wakefulness. The mechanism of such daytime carryover effects remains unclear. Repetitive apneas expose the cardiovascular system to exaggerated negative intrathoracic pressure, intermittent hypoxia, surges in SNA, and frequent awakenings (Bradley & Floras, 2009; Kasai et al., 2012; Somers et al., 2008).

Since the 1970s, an association between OSA and hypertension has been observed (Guilleminault, Tikian, & Demet, 1976; Kales et al., 1984). The most compelling evidence regarding the casual relation between OSA and hypertension comes from the Wisconsin Sleep Cohort Study (Peppard, Young, Palta, & Skatrud, 2000), in which persons with mild abnormalities in the apnea-hypopnea index had 42% greater odds of developing hypertension at follow-up. A linear relationship between the severity of sleep-disordered breathing and prevalence of hypertension

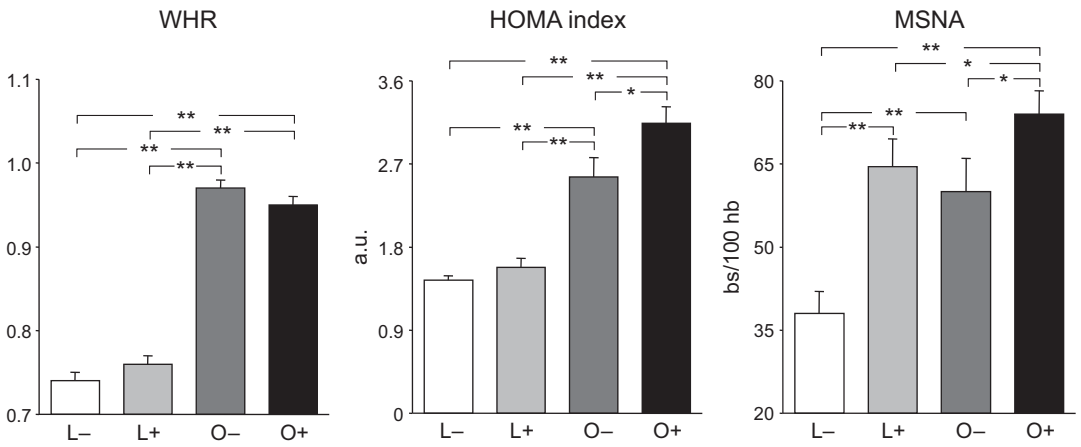

FIGURE 3 Waist-to-hip ratio (WHR), homeostatic model assessment (HOMA index), and muscle sympathetic nerve activity (MSNA) values detected lean subjects without (L–) and with (L+) sleep apnea and age-matched obese patients without (O–) and with (O+) sleep apnea. Data are shown as the means (±SEM). $*P<0.05$, $**P<0.01$. *Modified from Grassi, Facchini, et al. (2005).*

was found in the approximately 6000 patients in the Sleep Heart Health Study (Nieto et al., 2000). An animal model of OSA has provided strong evidence for its causal relationship with hypertension (Brooks, Horner, Kozar, Render-Teixeira, & Phillipson, 1997). When the risk of developing hypertension is expressed as an odds ratio, the range is from 1.3 to 9.7, depending on the population under study (Duran, Esnaola, Rubio, & Iztueta, 2001; Nieto et al., 2000). The risk of developing hypertension appears to be higher in young and nonobese subjects with severe OSA. We can speculate that a lower cardiovascular reactivity and the impairment in cardiovascular control mechanism that characterize elderly subjects might render them partly immune from the effects of repeated nocturnal airway obstruction and hypoxia, which increase blood pressure through a hypoxia-related impairment of the same mechanisms.

The association between obesity and hypersomnolence (the so-called "Pickwickian syndrome") was described in 1889, well before OSA was recognized (Auchincloss, Cook, & Renzetti, 1955; Burwell, Robin, & Whaley, 1956; Lavie, 2008). Increases in weight have been associated with an increasing prevalence of OSA. OSA seems to be much more common in patients who have class II and III obesity. A 10% weight gain predicts a 32% increase in the apnea-hypopnea index and a sixfold increase in the risk for developing moderate to severe OSA (Peppard et al., 2000). Obesity can affect the structure and function of the upper airway. In breathing, various forces promote airway collapse (see later). Upper-airway narrowing in obesity is dependent on the effects of subcutaneous and periluminal fat deposits of the pharynx. Central obesity (abdominal or visceral fat) seems to be one of the main risk factors for OSA. Recent studies, directly assessing sympathetic nervous system via microneurography, have been conducted to determine the contribution of the increased body weight, per se, versus OSA in producing sympathetic activation in human obesity. Comparing lean and obese subjects, both with or without OSA (Figure 3), it has been shown that sympathetic nerve activity was as follows: (1) greater in obese subjects without OSA than in lean subjects without OSA, (2) greater in obese subjects with OSA than in lean subjects with OSA, and (3) greater in subjects with than in those without OSA, regardless of the presence or absence of obesity. This allows us to conclude the following: (1) the sympathetic activation seen in human obesity occurs independently of OSA, (2) OSA has a sympathostimulating effect that is independent of body weight but additive to that displayed by the overweight state, and (3) the OSA-dependent and OSA-independent sympathostimulating effects contribute to the overall sympathetic hyperactivity of obesity (Grassi, Facchini, et al., 2005; Narkiewicz, van de Borne, Cooley, Dyken, & Somers, 1998).

A recent article from our group has documented that the sympathetic overdrive detectable in the OSA syndrome is not generalized to the entire cardiovascular system, given the evidence that the adrenergic activation found in the skeletal muscle vascular district is not paralleled by a concomitant and similar elevation in skin sympathetic nerve traffic (Grassi et al., 2014).

Intermittent apnea-related hypoxia and postapneic reoxygenation can induce oxidative stress with production of reactive oxygen species, which diminishes bioavailability of nitric oxide, and activation of inflammatory mediators possibly through the activation of nuclear transcriptional factors, which are capable of impairing vascular endothelial function. Indeed, patients with OSA have low plasma nitrite concentrations and high levels of oxidative stress markers. In addition, patients with OSA have greater blood levels of several inflammatory mediators (Budhiraja, Parthasarathy, & Quan, 2007; Carlson, Rangemark, & Hedner, 1996; Garvey, Taylor, & McNicholas, 2009).

Combined with increased sympathetic vasoconstrictor activity, all these factors could predispose to advanced endothelial dysfunction and, moreover, have the potential to accelerate atherogenesis.

MECHANISMS RESPONSIBLE FOR THE SYMPATHETIC ABNORMALITIES

The changes observed in sympathetic drive, such as those described in the metabolic syndrome and in its single components and in sleep apnea syndrome, are likely to have a multiple physiopathological nature (Figure 4). One of the hypotheses advanced is that the neurogenic alterations originate from an impairment of the baroreflex (i.e., a major restraining mechanism on sympathetic tone) (Grassi, 1998). This has been confirmed by the evidence that arterial baroreceptor control of sympathetic nerve traffic undergoes a clear-cut impairment in patients with metabolic syndrome and sleep apnea syndrome and that both the sympathoinhibitory and the sympathoexcitatory baroreflex components are involved (Grassi, Dell'Oro, et al., 2005). The reflex impairment may also involve other reflexogenic areas, such as the cardiopulmonary receptors and the chemoreceptors as well (Grassi, Dell'Oro, et al., 2005). Although no specific data are available on the behavior of these reflex functions in the metabolic syndrome, data collected in hypertensive patients with left ventricular hypertrophy or in obese subjects with sleep apnea syndrome do provide clear-cut evidence that alterations in the reflex restraint exerted by these reflexogenic areas on adrenergic drive may participate in the occurrence of the hyperadrenergic state (Grassi et al., 1988; Narkiewicz et al., 1999). It has also been hypothesized that the sympathetic overactivity occurring in the metabolic syndrome is dependent on the hyperinsulinemia and the related insulin resistance state characterizing the disease (Landsberg, 1996). This hypothesis comes from the evidence that acute systemic administration of insulin during a euglycemic clamp triggers a marked sympathetic stimulation (Anderson, Balon, Hoffman, Sinkey, & Mark, 1992; Landsberg, 1996; Scherrer & Sartori, 1997). Several lines of data support this hypothesis. There is a close correlation between the level of activation of the sympathetic nervous system and the level of insulin resistance in both cardiovascular and non-cardiovascular diseases. It has also been shown that the effects of antihypertensive drugs on adrenergic drive are frequently mirrored by their impact on insulin sensitivity. A further intriguing finding is that the sympathetic-insulin crosstalk is bidirectional, and at present, it is still unknown whether the sympathetic activation is responsible for the insulin resistance state or whether it represents an epiphenomenon of the metabolic alterations (Jamerson, Julius, Gudbrandsson, Andersson, & Brant, 1993; Landsberg, 1996).

Another possibility is that the sympathetic overactivity depends on the hormonal factors involved in the homeostatic control of the cardiovascular function. This is the case of angiotensin II and leptin. For example, angiotensin II enhances neuroadrenergic cardiovascular drive through stimulation of receptors located within the paraventricular nucleus of the hypothalamus, interacts with the nitric oxide system to potentiate sympathetic function, and affects norepinephrine turnover at the level of peripheral nerve endings (Grassi, 2001; Li, Wang, Mayhan, & Patel, 2006; Taddei & Grassi, 2005). This hypothesis appears to be confirmed in

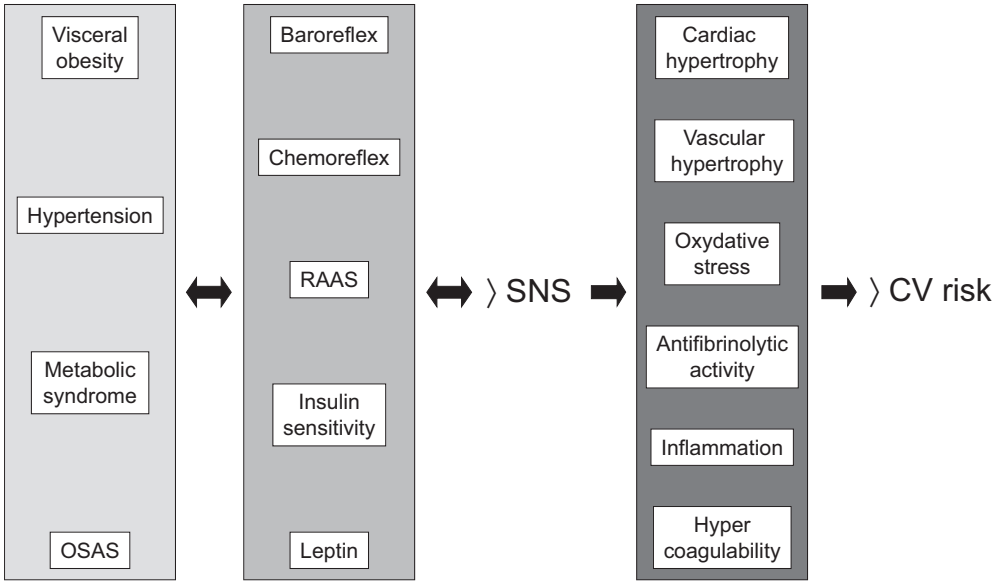

FIGURE 4 Schematic drawing illustrating the relationships between the different pathophysiological conditions, the mechanisms involved, the sympathetic overactivity, and its complications.

humans by the evidence that, in obese hypertensive patients, administration of angiotensin II receptor blockers results in a clear-cut sympathoinhibition (Grassi et al., 2003). A further hormonal substance is leptin, which acts at the level of the hypothalamus to increase blood pressure via its central sympathoexcitatory effects (Grassi, 2004; Rahmouni, Correia, Haynes, & Mark, 2005).

SYMPATHETIC ACTIVATION AND CARDIOVASCULAR RISK

The sympathetic activation observed in metabolic syndrome and sleep apnea syndrome can alter cardiovascular structure and function by increasing blood pressure or through direct influences (Mancia et al., 1999). In vitro, adrenergic agents are able to enhance cardiac cell growth and the replication of vascular smooth muscle cells, thus favoring cardiac hypertrophy and hyperplasia of muscle tissue in the vascular wall (Johnson, Grignolo, Kuhn, & Schanberg, 1983). This is in line with evidence from animal models. The prolonged infusion of catecholamines at subpressor doses causes an increase in cardiac mass and atherosclerosis, whereas carotid artery denervation leads to a reduction in vascular wall thickness compared with the contralateral intact vessel (Yamori et al., 1984). Sympathetic factors may also contribute to the arterial stiffening seen in these pathophysiological conditions because several lines of data provide evidence that the arterial distensibility of middle-sized and large elastic arteries is reduced by sympathetic tone (Giannattasio & Mancia, 2002). The mechanism responsible could be the contraction of smooth muscle in the arterial wall, given that the elastic modulus of the contracted vessel is greater than that of the relaxed vessel (Giannattasio & Mancia, 2002).

Also, OSA-associated disturbances, especially chronic intermittent hypoxia and enhanced sympathetic activity, lead to up-regulation of the renin-angiotensin system and down-regulation of nitric oxide synthases (Prabhakar, Fields, Baker, & Fletcher, 2001). Cyclic intermittent hypoxia may lead to sympathoexcitation via two mechanisms: augmentation of peripheral chemoreflex sensitivity and direct effects on sites of central regulation. Human studies have shown that intermittent hypoxia increases sympathetic activity, blood pressure levels, antifibrinolytic activity (elevation in plasminogen activator inhibition type 1), oxidative stress (activation of reduction–oxidation-sensitive gene expression is suggested by the increase in some protein products of these genes, including vascular endothelial growth factor, erythropoietin, and endothelin-1), inflammatory mediators (tumor necrosis factor-α, interleukin 6, T lymphocyte, and pentraxin), and hypercoagulability (Arias et al., 2008; Belaidi et al., 2009; Guzik et al., 2007; Kasai et al., 2011; Steiropoulos et al., 2009). All these factors contribute to increase the risk for cardiovascular diseases in complicated obesity and sleep apnea syndrome (Figure 4).

THERAPEUTIC IMPLICATIONS

Dietary weight loss is the most common and simplest treatment of obesity, metabolic syndrome, and obesity complicated by OSA. However, this approach has not been an effective long-term method, with a success rate of only 15% during a prolonged follow-up (Ayyad & Andersen, 2000). Because the visceral fat is associated with detrimental metabolic consequences, it seems that even a modest weight loss (7–10% of body weight) may induce significant metabolic advantages and reduce the hyperadrenergic tone (Grassi, Seravalle, et al., 1998; Pasanisi, Contaldo, de Simone, & Mancini, 2001). In addition to these beneficial effects, subjects exposed to lifestyle modifications and low-caloric diets have shown a reduction in the incidence of new-onset diabetes and a reduction in the risk of developing hypertension, thereby offsetting two major risk factors in individuals highly predisposable to metabolic syndrome (Grundy et al., 2005; Knowler et al., 2002). Lifestyle modifications favorably affect the sympathetic overactivity characterizing the metabolic syndrome, as well as its components, both with or without the presence of OSA. In obese subjects exposed to 16 weeks of restricted diet, a modest reduction in body weight was accompanied by a marked reduction in muscle sympathetic nerve activity with a concomitant recovery of the impaired baroreflex ability to modulate sympathetic tone (Grassi, Seravelle, et al., 1998). These data are in line with those collected in patients affected by metabolic syndrome by Straznicky et al. (2005), in which a hypocaloric diet-induced 7% reduction in body weight was able to reduce the norepinephrine spillover rate and muscle sympathetic nerve activity and enhance the baroreflex ability to modulate the sinus node activity and improve the metabolic syndrome components.

Different approaches could be applied to obtain weight loss and sympathetic inhibition. Regarding the first one, studies with the serotonin-norepinephrine reuptake inhibitor sibutramine, capable of suppressing appetite, have shown to be modestly effective (5% greater weight loss than placebo) (Li et al., 2005). Furthermore, sibutramine may contribute to systemic arterial hypertension and cardiac arrhythmias because of its adrenergic activity, thus showing it not to be safe for patients with sleep-disordered breathing and predisposed to these complications. A drug treatment approach could be also recommended both to induce a weight loss and to treat the metabolic syndrome components to obtain a cardiovascular protective effect (Grundy et al., 2005).

Other drugs have not shown positive results because of the secondary negative effects. This is the case for the selective antagonist of CB1 receptors rimonabant, which was able to induce a significant weight loss and an improvement in metabolic parameters; however, this effect was accompanied by an increase in depressive effects (Gadde & Allison, 2006). New promising drugs under investigation are based on the effects on the leptin/adiponectin balance or on stimulation of 5-HT2C serotoninergic receptors located in the brain.

A different approach is based on bariatric surgery that is now more commonly done because of the significant increase in the prevalence of obesity and complicated obesity. The National Heart, Lung, and Blood Institute guidelines recommend bariatric surgery to achieve weight loss if the patient's body mass index (BMI) is ≥40 or ≥35 in the presence of significant comorbidities. Bariatric surgery modifies the gastrointestinal tract and reduces the intake of nutrients by decreasing the capacity of the gastric pouch or inducing malabsorption (Kiernan & Winkleby, 2000).

A study performed by our group has shown that 6 months after sleeve gastrectomy, a significant ($P<0.05$) reduction was observed in BMI, and this was accompanied by a better blood pressure profile and improvement in insulin sensitivity that showed a tendency to return toward presurgery values in the long-term period. An improvement was also observed in adrenergic tone and in baroreflex control of muscle sympathetic nerve activity (Seravalle et al., 2011). These data provide evidence that massive weight loss induced by sleeve gastrectomy triggers profound sympathoinhibitory and eumetabolic effects, which appear to follow a different time course, suggesting their independent behavior. In the long-term period, the weight loss-related sympathoinhibition appears dependent on the body weight loss "per se" and on the improvement in the baroreflex–muscle sympathetic nerve activity control, rather than on the changes in insulin sensitivity.

Bariatric surgery is the most effective weight-loss therapy for morbidly obese patients. This approach is able to improve sleep-disordered breathing in most patients and has a relatively low mortality rate.

Several studies have reported the impact of continuous positive airway pressure (CPAP) therapy for OSA in obesity. Adherence to this therapy facilitates weight loss. Six months of CPAP therapy is able to reduce the amounts of intra-abdominal visceral fat, even in absence of weight loss and decreased serum leptin levels. This decrease in serum leptin levels could also facilitate weight loss through decreased caloric intake (Chin et al., 1999).

Randomized trials have also shown that CPAP therapy for OSA resulted in a significant improvement in endothelial function and arterial stiffness. Recent observational studies showed that short-term CPAP therapy can reduce arterial stiffness parameters in association with reduction of SNA and that long-term (>1-year) CPAP therapy can retard progression of arterial stiffness (Drager, Bortolotto, Figueiredo, Krieger, & Lorenzi-Filho, 2007). As a consequence of such OSA-related atherogenesis, patients with OSA are likely to have coronary artery disease and ischemic cardiomyopathy.

Several experimental studies suggested that OSA can induce an increase in blood pressure (BP) levels. In patients with OSA, a physiological decrease in nighttime BP is often lacking in association with nocturnal sympathetic activation and a consequent increase in BP (Ancoli-Israel et al., 2002; Cano-Pumarega et al., 2011; Peppard et al., 2000).

There is also evidence that indicates the association between drug-resistant hypertension and OSA (Calhoun et al., 2008). Two cross-sectional studies demonstrate that the more severe the OSA, the less likely blood pressure could be controlled despite increasing the number of antihypertensive agents (Grote, Hedner, & Peter, 2000; Lavie & Hoffstein, 2001). OSA is extremely common in subjects with resistant hypertension, and a significant correlation between plasma aldosterone concentration and OSA severity has been observed in subjects with resistant hypertension but not in control subjects, suggesting that aldosterone excess may contribute to OSA severity (Pratt-Ubunama et al., 2007).

Thus, because sympathetic deactivation should be one of the goals of pharmacological interventions in obesity, complicated obesity, and metabolic syndrome, a positive effect could be also obtained by the antihypertensive drug treatment that is frequently part of the therapeutic approach of these patients. Although diuretics and β-blocking agents appear to be contraindicated because of their unfavorable metabolic effects, calcium channels blockers, angiotensin-converting enzyme inhibitors, and angiotensin II antagonists represent the first choice because these drugs (1) are effective in ensuring a blood pressure control over a 24-h period, (2) have a neutral effect on lipid profile, (3) improve insulin sensitivity, and (4) exert neutral or favorable effects on sympathetic function. The inhibition of the sympathoexcitatory effects of angiotensin II has been confirmed by our group in a study in which a consistent reduction in sympathetic nerve traffic was detected in obese hypertensive subjects after a 12-week administration of an angiotensin II receptor antagonist (Grassi et al., 2003). A more direct and powerful sympathoinhibition can also be achieved by new central sympatholitic agents, such as imidazoline I_1 receptor agonists. This recently developed class of drugs, which includes moxonidine and rilmenidine, exerts central sympathoinhibition by stimulating type 1 imidazoline receptors located in the rostroventromedullary region of the brain stem. These drugs have shown favorable effects on insulin sensitivity, glucose tolerance, and lipid profile in subjects affected by metabolic syndrome (van Zwieten, 2001).

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Chapter 19

Obstructive Sleep Apnea and the Metabolic Syndrome: Pathophysiological and Clinical Evidence

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INTRODUCTION

Obstructive sleep apnea syndrome (OSAS) is a common nocturnal disorder characterized by the presence of repetitive apnea and hypopnea during sleep, daytime sleepiness, and cardiopulmonary dysfunction. Patients with OSAS experience recurrent episodes of cessation of breathing that expose the cardiovascular system to cycles of hypoxia, exaggerated negative intrathoracic pressure, and arousals. The number of apneas and hypopneas per hour of sleep is termed the apnea-hypopnea index (AHI) and has been used as a marker of OSA severity. An OSA disorder is generally defined as five or more apneas or hypopneas per hour of sleep. Moderate and severe OSA are defined as AHI ≥ 15 and ≥30, respectively.

EPIDEMIOLOGY OF OSAS

OSAS is a common condition affecting at least 1–5% of middle-aged individuals in various ethnic populations. OSA has an increasing prevalence worldwide.

Approximately 13% of men and 6% of women between 30 and 70 years of age have moderate to severe forms of OSA. Present data show an impressive increase in the prevalence of OSA in the last decades (Peppard et al., 2013). Prevalence of OSA may reach up to 50% in obese people. Moreover, 60% of patients with metabolic syndrome (MetS) have OSA and this prevalence is even higher in obese patients with diabetes (Angelico et al., 2010). Notably, many studies demonstrated that successful treatment of OSA helps better control many of the associated diseases and chronic conditions.

Most patients with OSA syndrome remain undiagnosed, and the recognition of this condition is poor even in people with obesity or hypertension.

OSAS AND CARDIOVASCULAR DISEASES

Sleep-related breathing disorders are highly prevalent in patients with established cardiovascular disease (CVD). In particular, the prevalence of OSA is higher in populations with hypertension, heart failure, ischemic heart disease, and stroke.

Multiple comorbidities, such as obesity, hypertension, CVD, and MetS, are present in the majority of patients with sleep apnea (Angelico et al., 2010). Hence, it is difficult to understand whether abnormalities evident in the OSA

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patient with CVD are secondary to the sleep apnea, the cardiovascular condition, or both.

Observational studies suggest OSA as an important cardiovascular risk factor for incident ischemic heart disease, stroke, and CVD-caused mortality. In fact, several clinic-based longitudinal studies have found an association between OSA and the development of coronary artery disease (CAD), after adjusting for other risk factors, mainly in untreated individuals referred to continuous positive airway pressure (CPAP) treatment.

Currently, OSAS is also considered an independent risk factor for stroke. In particular, in an observational cohort study, an independent association between OSA and a combination of stroke and death was reported (Yaggy et al., 2005). Furthermore, the risk was found to increase with higher severity of OSA.

OSA interrupts the cardiovascular quiescence typical of sleep by triggering a cascade of acute hemodynamic, autonomic, chemical, inflammatory, and metabolic effects, these alterations cause chronic aftereffects capable of initiating or exacerbating CVD.

Thus, OSA can exacerbate CVD by many different mechanisms. Ineffectual inspiratory efforts typical of OSAS cause negative intrathoracic pressure that, by hemodynamic mechanisms, may impede left ventricular filling and decrease stroke volume. Moreover, hypoxia during OSA might also directly impair cardiac contractility and diastolic relaxation. Besides, intermittent hypoxia can even induce the production of oxygen free radicals and activate inflammatory pathways that impair vascular endothelial function and increase blood pressure. It has been demonstrated that OSA can also promote oxidation of lipoproteins, increase the expression of adhesion molecules, promote monocyte adherence to endothelial cells, and induce vascular smooth-muscle cells proliferation. Notably, platelet activation and aggregability, markers of increased susceptibility to thrombosis, are increased during sleep in patients with OSA, and morning fibrinogen concentration is increased and plasminogen activator inhibitor type-1 activity is decreased (Steiner et al., 2005).

These adverse events, combined with increased sympathetic vasoconstrictor activity and inflammation, could predispose to hypertension and atherosclerosis. Finally, cerebral blood flow declines significantly during the episodes of obstructive apnea due to a decrease in cardiac output; so in patients with flow-limiting lesions of the cerebral arteries, this can further predispose to ischemic events (Balfors & Franklin, 1994).

DEFINITION AND CLINICAL PRESENTATION OF METS

Clustering of cardiovascular risk factors (termed "the metabolic syndrome" in 1981) was recognized as early as the 1920s and is currently thought to be related to the underlying pathophysiology of insulin resistance and hyperinsulinemia. MetS represents a constellation of metabolic derangements, including central obesity, hypertension, glucose intolerance, and dyslipidemia. It is a well-recognized risk factor for CVD and type 2 diabetes. Obesity increases the likelihood that this cluster of abnormalities will occur.

In 2001, the National Cholesterol Education Program Adult Treatment Panel III report (ATP III) recommended the use of five variables, with established diagnostic cutoffs, to define MetS: abdominal obesity, hypertension, insulin resistance or glucose intolerance, low serum high-density lipoprotein (HDL) cholesterol, and elevated serum triglycerides. Any individuals satisfying three of these five criteria would be classified as having MetS. The International Diabetes Federation (IDF) criteria included the same five components as the ATP III version, but indicated that one abnormality had to be present to diagnose MetS; namely, abdominal obesity, as assessed by measuring waist circumference. An enlarged waist circumference, and any two of the remaining four components were sufficient to diagnose MetS. More recently, ATP III and the IDF, joined by several other prestigious organizations, have proposed a "harmonized" definition of MetS, including different ethnic threshold criteria for waist circumference definition of abdominal obesity (Eckel, 2010). In this "working" definition, all criteria are clinically identifiable, thus making it easy to recognize MetS in practice. However, since different clinical and biochemical criteria may be proposed for the definition of MetS, using the broad clinical criteria, the diagnosis of MetS is very common and patients may have a different clustering of risk factors and present various degrees of insulin resistance and secretion. Moreover, MetS may have multiple clinical and pathophysiological presentations and among them, most important, its presentation with or without diabetes. The goal of diagnosing MetS is to identify persons at increased risk of CVD and type 2 diabetes.

OSAS AND METS

Current data suggest that there is an increased prevalence of MetS in subjects with OSA. Many epidemiological and clinical studies have demonstrated independent associations of OSA with MetS (Coughlin, Mawdsley, Mugarza, Calverley, & Wilding, 2004; Sasanabe et al., 2006). In fact, the majority of OSAS patients show the cluster of metabolic and non-metabolic cardiovascular risk factors of MetS, including also proinflammatory and prothrombotic states and increased systemic oxidative stress. It appears that more than two-thirds of severe OSA (AHI≥30) patients have MetS in both Eastern and Western countries. Moreover, the prevalence of MetS is increasing with the epidemic of obesity across different ethnic origins. For these reasons, it has been suggested that OSA may be a further manifestation of MetS. Syndrome Z (Wilcox, McNamara,

Collins, Grunstein, & Sullivan, 1998) is defined as the co-occurrence of OSA and MetS.

There are a number of possible reasons why OSA may be independently associated with an increase in the clinical and biochemical features typical of MetS. It is possible that OSA either directly increases these factors, or that OSA and MetS share common risk factors. In particular, it has been suggested that this association may be due to the relation of OSAS and MetS with obesity. However, although MetS and OSA may simply be coincident syndromes, there is growing, albeit inconclusive, evidence that the pathophysiology of OSA and MetS may overlap considerably. Moreover, an independent association of OSAS with the individual risk factors of MetS seems to be present. In fact, it is also possible that OSAS might directly contribute to the development of insulin resistance and the other cardiovascular risk factors found in patients with MetS. Therefore, based on these considerations, a model of bidirectional association between OSA and MetS may be proposed.

In a previous study performed by our group in a large series of heavy snorers, a strong association between OSAS, MetS, and its clinical and metabolic components was found in subjects of both sexes examined in an internal medicine setting (Angelico et al., 2010). Patients with severe OSA were more obese, more hypertensive, and more insulin resistant than those with a less severe OSA and control snorers. Polysomnographic indices – AHI, ODI, and average SaO2 – were independent predictors of central obesity, serum insulin, and the metabolic score, i.e., the number of components of MetS. In particular, an independent association was found between ODI and insulin resistance (HOMA-IR), which is generally believed to play a central role in the clustering phenomenon of CVD risk factors that defines MetS. The concurrent presence of MetS and OSA may have an additive effect on atherosclerosis.

OSAS AND CENTRAL OBESITY

Most patients with newly diagnosed OSA have a history of excessive weight gain in the period preceding the diagnosis. Obesity is an important risk factor for the development of OSA. Prevalence of OSA is probably rising as a consequence of increasing obesity. The mechanisms of this association are probably multifactorial. In fact, obese people have extrinsic narrowing of the area surrounding the collapsible region of the pharynx and regional soft tissue enlargement; moreover, they have also increased neck circumference and fat deposits posterolateral to oropharyngeal airspace at the level of soft palate, in the soft palate, and in submental area.

Sleep apnea patients have a greater amount of visceral fat compared with obese controls matched for BMI, suggesting that central or abdominal obesity are more closely associated with OSA than general obesity. Moreover, central adiposity and visceral fat deposition also appear to be the hallmark of increased risk for OSA. Obesity also plays a vital role in the pathogenesis of the core feature of MetS, insulin resistance, which in turn may induce OSA.

OSAS AND ARTERIAL HYPERTENSION

Epidemiological studies have shown that approximately 40% of patients with sleep apnea have hypertension, and that about 40% of patients with hypertension have sleep apnea (Nieto et al., 2000; Young et al., 1993). Sleep-related breathing disorders are common contributing factors to the production of essential hypertension but are neglected, underdiagnosed, and undertreated. Evidence that OSA can cause elevated blood pressure levels during sleep and during the day is very strong. In fact, several reports have shown that the prevalence of hypertension is greater in patients with OSA and vice versa (Wolk, Shamsuzzaman, & Somers, 2003). Actual figures vary, depending on the definitions and thresholds for sleep apnea and hypertension. Moreover, severity of OSA is correlated with the presence of hypertension (Steinhorst et al., 2013).

Recent guidelines for the management of arterial hypertension recognized OSA as an identifiable and not uncommon cause of resistant hypertension (Mancia et al., 2007). OSAS is an independent risk factor for hypertension, and hypertension is a frequent comorbid condition with sleep apnea. Compared with controls, OSA patients have higher blood pressure and heart rate, and a reduction of the sleep-related nocturnal blood pressure drop. In fact, repetitive episodes of airway occlusion and hypoxemia induce paradoxical rises in blood pressure during sleep. Moreover, patients with OSA do not manifest the usual fall in mean arterial blood pressures during sleep and have a non-dipper 24 h blood pressure profile.

OSA may have a causal role in the development of hypertension. In the Wisconsin Sleep Cohort Study, an independent dose–response relation between sleep-disordered breathing at baseline and the development of new hypertension 4 years later was demonstrated. The odds ratios for the presence of incident hypertension at follow-up were 1.42, 2.03, and 2.89 with an AHI of <5, 5 to 15, and >15 events per hour at baseline, respectively.

Furthermore, there is a growing experimental evidence that OSA can cause blood pressure rise, by increasing the activation of the renin-angiotensin system (Peppard et al., 2013). This hypothesis has been strengthened by evidence from intervention trials showing that treatment with CPAP may lower both systolic and diastolic blood pressures. OSA may also cause acute nocturnal surges in blood pressure in response to chemoreflex-mediated hypoxic stimulation of sympathetic activity and in part, may contribute to the nocturnal "non-dipping" pattern of hypertension. Therefore, sleep deprivation is itself now being understood as

an important cause of neural, vascular, and endocrine disruption, leading to increases in blood pressure. All these findings suggest that OSA is likely to be a risk factor for hypertension and consequent cardiovascular morbidity in the general population.

OSAS, INSULIN RESISTANCE AND DIABETES

Insulin resistance is the hallmark and key feature of MetS, which may predispose to type 2 diabetes, atherogenic dyslipidemia fatty liver infiltration, and increased global cardiovascular risk. It is estimated that 34% of adult Americans have insulin resistance as a result of the increased prevalence of obesity and sedentary lifestyles. It is unknown whether OSA contributes to insulin resistance, although it has been suggested that the intermittent hypoxia associated with sleep apnea may cause a drop in insulin sensitivity.

Patients with severe OSA are more insulin resistant than those with a less severe OSA and control snorers (Angelico et al., 2010).

Rates of OSA are much higher among people with type 2 diabetes. In people who have diabetes, the prevalence of OSA may be up to 23%. At the same time, rates of diabetes are higher among people with OSA. The two diseases also share risk factors, including obesity and advancing age. However, it has been proposed that OSA and type 2 diabetes mellitus may be associated independently of the degree of adiposity and that OSA may be a risk factor for diabetes mellitus. By contrast, a longitudinal study of 1300 subjects in the Wisconsin Sleep Cohort did not find any independent relationship between OSA and incident diabetes at 4-year follow-up, despite a higher prevalence of diabetes in OSA subjects independent of other risk factors at baseline (Reichmuth, Austin, Skatrud, & Young, 2005).

Several pathophysiologic mechanisms have been proposed to explain the alterations in glucose metabolism in OSA patients. Intermittent hypoxia, endothelial dysfunction, inflammatory state, sleep fragmentation, and high sympathetic nervous system activity all can play a pivotal role in the dysregulation of glucose control. Poor sleep quality and intermittent hypoxemia from OSA may serve as the catalyst for glucose dysregulation. Over time, these abnormalities may accelerate weight gain, which may increase the severity of OSA. Moreover, it should be taken in to account that many patients with type 2 diabetes have undiagnosed OSA. Finally, it should be considered that most diabetic OSA patients satisfy the criteria for MetS and are affected by hypertension and central obesity. In fact, in our study of heavy snorers, more than 90% of diabetic OSA patients satisfied the criteria for MetS and were affected by hypertension and central obesity, while the corresponding figures in non-diabetic OSA were 54.0%, 67.8%, and 80.9% respectively (Angelico et al., 2010).

OSAS AND ATHEROGENIC DYSLIPIDEMIA

Few cross-sectional studies suggested that OSA is independently associated with hyperlipidemia. In subjects with OSA, a higher prevalence of dyslipidemia was found after adjustment for BMI (McArdle, Hillman, Beilin, & Watts, 2007) and AHI was independently associated with low HDL levels (Borgel et al., 2006). Elevations in total cholesterol, triglycerides, and corresponding reduction in HDL have been coupled to oxidative processes commonly found in OSA (Li et al., 2007). Moreover, it has been suggested that hypersympathetic tone and oxidative stress induced by OSA may have adverse impact on cholesterol metabolism via generation of stearoyl-coenzyme A desaturase-1, reactive oxygen species (ROS), peroxidation of lipids, as well as systemic inflammation (Adedayo et al., 2012).

OSAS AND INFLAMMATION

A number of markers of systemic inflammation are elevated in patients with OSA; they include tumor necrosis factor alpha (TNF-a), IL-6, and C-reactive protein (CRP) (Punjabi & Beamer, 2007). Patients with OSA have also decreased levels of anti-inflammatory substances, including IL-10 and adiponectin. OSA itself further exacerbates systemic inflammation especially in obese patients. In fact, OSA may initiate a cascade of events that may promote the activation of macrophages and subsequent release of proinflammatory cytokines.

Several studies demonstrated higher serum levels of TNF-a in subjects with OSA than in subjects without OSA (Ciftci, Kokturk, Bukan, & Bilgihan, 2004; Kanbay, Kokturk, Ciftci, Tavil, & Bukan, 2008), whereas other studies did not find significant differences between OSAS patients and their matched control group (Vgontzas et al., 2000).

Many other cytokines/adipokines involved in the development of atherogenesis were also investigated in patients with OSAS, including IL-6, IL-8, IL-12, IL-18, and γ-interferon.

IL-6 is a major initiator of the acute-phase response and the main regulator of hepatic CRP production. Moreover, IL-6 is produced by a variety of cells, is predictive of future cardiovascular events, and is expressed in human atherosclerotic lesions (Luc et al., 2003). However, there are conflicting reports in the literature regarding both IL-6 levels and CRP levels in the circulation of patients with OSAS. In fact, while some studies report increased levels of CRP or IL-6 in OSAS, others have shown that obesity rather than OSAS severity was associated with systemic inflammation.

OSAS AND OXIDATIVE STRESS

Several studies have provided evidence supporting an increase of systemic oxidative stress in OSAS (Barcelò et al., 2000; Carpagnano et al., 2003; Del Ben et al., 2012;

Katsoulis, Kontakiotis, & Spanogiannis, 2011). Oxidative stress is characterized by an imbalance between oxidant and antioxidant mechanisms, in which many different enzymatic and non-enzymatic antioxidants take place. It has been postulated that intermittent hypoxia and reoxygenation can induce ROS generation, which may lead to chronic inflammation, endothelial dysfunction, and increased cardiovascular risk. In fact, in hypoxic reoxygenation conditions, mitochondria becomes dysfunctional to produce even higher amounts of ROS.

Increased oxidative stress in OSA has been primarily shown by using various markers of lipid peroxidation in plasma and urines. Urinary isoprostanes, a reliable marker of lipoperoxidation, correlate best to the average desaturation index in OSA, which suggests that they are reliable biomarkers for chronic intermittent hypoxia and oxidative stress (Del Ben et al., 2012). An open question is whether OSA itself results in oxidative stress or it is simply a consequence of metabolic comorbidities frequently associated to OSAS. In a study performed in otherwise healthy OSA patients, without any other comorbidities, no evidence for higher oxidative stress and lipid peroxidation was observed (Svatikova et al., 2005). By contrast, we provided evidence that patients with MetS have endothelial dysfunction and increased systemic oxidative stress (Del Ben et al., 2012). In fact, in our series of consecutive patients with heavy snoring, those with severe OSAS had higher levels of urinary 8-iso-PGF2α and serum NOX2, a ROS generating enzyme and lower NOx, stable NO derivatives, reflecting overall NO production.

OSAS AND ENDOTHELIAL DYSFUNCTION

Oxidative stress is a major component in the initiation and development of endothelial dysfunction, which depends on the reduction in NO bioavailability and is widely accepted as an early marker of atherosclerosis.

Recent studies suggest that the repetitive episodes of hypoxia and reoxygenation could promote the activation of proinflammatory pathways and disrupt normal endothelial function by mechanisms similar to those of the ischemia/reperfusion injury model. Moreover, previous studies have demonstrated that total nitrate and nitrite (NOx) production is lower in OSAS patients than in controls (Del Ben et al., 2012).

Flow-mediated, brachial artery vasodilation (FMD) is a well-established marker of endothelial function, as the result of endothelial release of NO. Endothelial dysfunction is markedly reduced in patients with moderate/severe OSAS and in those with MetS (Angelico et al., 2011; Del Ben et al., 2012; Del Ben, Loffredo, Violi, & Angelico, 2013).

FMD is impaired in subjects with OSA independently of obesity and conventional risk factors (Namtvedt et al., 2013) and in the absence of known CVD (Jones et al., 2013).

Subjects with major overnight oxygen desaturation show significant impairment in both endothelium-dependent and -independent vasodilatation in response to intra-arterial infusion of acetylcholine and sodium nitroprusside, respectively (Cross et al., 2008).

However, even in those OSA subjects with minimal symptoms, endothelial function has been shown to be impaired (Kohler et al., 2008).

A recent study found that when regression analysis was limited to the subgroup of subjects less than 50 years old, OSA was the only independent predictor of FMD, replacing age. Thus, the authors concluded that OSA may exert a "premature aging effect" on endothelial function (Yim-Yeh et al., 2010).

CPAP AND MetS

Cardiovascular complications in OSAS are multifactorial, and involve alterations of endothelial dysfunction, inflammation, oxidative stress, and insulin resistance as a consequence of intermittent episodes of hypoxia and reoxygenation. Therefore, CPAP therapy may play an important role in reversing the above alterations and reducing high cardiovascular risk, particularly in patients with MetS. In fact, it has been reported that treatment with CPAP ameliorates oxygen desaturation and decreases CV morbidity and mortality (Doherty, Kiely, Swan, & McNicholas, 2005; Marin, Carrizo, Vicente, & Agusti, 2005). However, although nasal CPAP is highly effective in controlling OSAS, compliance data show only moderately satisfactory results. Moreover, obesity and visceral fat distribution may represent important confounding variables in this context.

Whether CPAP might be a novel method to reverse MetS in patients with OSA is a matter of debate. A recent paper in the New England Journal of Medicine (Sharma et al., 2011), claimed to show that CPAP can reverse MetS. In fact, in a double-blind, placebo-controlled trial, 3 months of CPAP therapy was able to lower blood pressure and partially reverse metabolic abnormalities, leading to a dramatic reversal of MetS among 11 of 86 treated patients. However, after a request to see the primary data, which had mysteriously gone missing, the authors retracted the article (Sharma et al., 2013).

Treatment with CPAP improves some components of MetS. Notably, it lowers blood pressure in patients with OSA. This effect is modest but consistent, and is more evident in patient with more severe hypertension. Two recent randomized studies comparing therapeutic and sub-therapeutic CPAP showed that blood pressure in those individuals receiving therapeutic CPAP was significantly lower, both at night and during the daytime. A meta-analysis of placebo-controlled, randomized trials confirmed greater reductions in ambulatory mean blood

pressure among patients with more severe OSA and better effective nocturnal use of CPAP device (Haentijens et al., 2007).

Whether CPAP treatment of OSA can reverse insulin resistance and prevent body weight gain is controversial. Some studies showed decreases of blood pressure and oxidative stress without relevant changes in insulin resistance in patients treated with CPAP (Murri et al., 2011). Conversely, a recent meta-analysis of randomized control trials showed a favorable effect of CPAP on insulin resistance as measured by HOMA-IR in patients with OSA without diabetes (Iftikhar, Khan, Das, & Magalang, 2013).

Interventional data regarding glucose metabolism in OSA have also shown conflicting results. In a small study using the hyperinsulinemic euglycemic clamp, CPAP was found to improve insulin sensitivity (Harsch et al., 2004), and in a further study, CPAP treatment reduced HOMA-IR in sleepy but not in non-sleepy OSA subjects with similar AHI levels (Barcelò et al., 2000). By contrast, a study of diabetic men with OSA showed no change in insulin sensitivity during 3 months of CPAP treatment compared with sham CPAP (West, Nicoll, Wallace, Matthews, & Stradling, 2007), and similarly, a crossover study of non-diabetic OSA men found no change in HOMA-IR during 6 weeks of CPAP treatment.

A few observational studies reported that nasal CPAP treatment improved serum lipid parameters. However, to date, there are no consistent data from randomized, controlled studies to support that treatment of OSA can modify dyslipidemia.

CPAP treatment is able to reduce oxidative stress in patients with OSA (Carpagnano et al., 2003). CPAP treatment significantly inhibited lipid peroxidation levels in hypertensives with severe OSA (Alzoghaibi & Bahammam, 2012), and plasma 8-isoprostanes decreased and NOx increased after effective CPAP (Del Ben et al., 2012).

Few data on the effects of CPAP on inflammation have been reported. One-month CPAP significantly decreased levels of both CRP and IL-6 and spontaneous IL-6 production by monocytes in patients with mild to moderate OSAS (Yokoe et al., 2003). CPAP treatment was also reported to increase serum adiponectin (Carneiro 2009) and to decrease serum leptin levels significantly (Chin et al., 1999).

Recently, CPAP therapy improved endothelial dysfunction and decreased the levels of oxidative stress and inflammatory cytokines in patients with MetS (Del Ben et al., 2012).

Long-term compliance to nasal CPAP (NCPAP) therapy was found to be effective in reducing the levels of systemic oxidative stress and improving endothelial dysfunction (Cross et al., 2008). In fact, NCPAP therapy normalized urinary 8-iso-PGF2α and serum sNOX2-dp values and increased flow-mediated brachial artery dilation even though there was no significant change in body weight or cardiovascular risk factors during the 6 months of treatment (Del Ben et al., 2012).

CONCLUSIONS

Based on current evidence, clinicians need to address the risk of OSA in patients with MetS and, conversely, evaluate the presence of MetS in patients with OSA. In fact, it is possible that the relationship goes in both directions. The concurrent presence of MetS and OSAS may have an additive effect on atherosclerosis. Early detection and treatment of OSAS in asymptomatic hypertensive patients is essentially important to prevent hypertensive target organ damage and cardiovascular events. Finally, weight loss should be recommended for all overweight or obese patients with sleep apnea, as it has also many beneficial effects on the metabolic profile in OSA subjects.

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Chapter 20

Sleep Deprivation and Metabolic Syndrome

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INTRODUCTION

Sleep deprivation (SD) due to voluntary bedtime restriction is a hallmark of Western society as a consequence of the modern lifestyle. In developed countries, people, on average, sleep only 6.8 hours per night, corresponding to 1.5 h less than a century ago (Nagai, Hoshide, & Kario, 2010); moreover, other studies have demonstrated that self-reported sleep duration <7 hours per night in young adults has increased from 15.6% in 1960 to 37.1% in 2001–2002 (Kripke, Simons, Garfinkel, & Hammond, 1979).

During the past 40 years, there has been a considerable increase in the incidence of obesity and diabetes, which are components of metabolic syndrome (MS) (Flegal, Carroll, Ogden, & Johnson, 2002). MS is a collection of cardiometabolic risk factors, including obesity, insulin resistance, hypertension, and dyslipidemia (Table 1).

Also, pathological conditions, such as insomnia and sleep-disordered breathing (SDB), may lead to chronic sleep loss. Although SDB is characterized by sleep fragmentation, respiratory tract disorders, and hypoxic stress, in addition to sleep loss itself, a decreased sleep time is a common feature. Recent studies have provided some evidence about the association between SD and the development of hypertension, obesity, and diabetes mellitus. In this chapter, our aim is to analyze the relationship between SD and the main components of MS.

SD AND HYPERTENSION

Experimental and clinical studies have recently reported an association between SD and higher incidence of arterial hypertension. Sleep has important homeostatic functions inhibiting stress and proinflammatory systems. For this reason, SD has been associated with impairments in sympathetic nervous system activation, stress system function, and proinflammatory pathways (Gangwisch et al., 2006; Meerlo, Sgoifo, & Suchecki, 2008). Chronic stress seems to play a noteworthy role in the pathophysiological association between SD and arterial hypertension; indeed, chronic stress may produce physiological alterations both directly and indirectly through sleep alterations and subsequent reduction of slow-wave sleep (SWS) (Palagini et al., 2013). Pathophysiological mechanisms leading to the development of arterial hypertension are thought to be (Figure 1):

1. Dysregulation of neuroendocrine stress system (hypothalamic-pituitary-adrenal (HPA) axis and sympathetic adrenal medullary axis): the activation of the neuroendocrine systems is transient after occasional sleep losses

Modulation of Sleep by Obesity, Diabetes, Age, and Diet. http://dx.doi.org/10.1016/B978-0-12-420168-2.00020-X

TABLE 1 Clinical Criteria for the Definition of Metabolic Syndrome According to the Adult Treatment Panel III

At least 3 of the following risk factors:

- Abdominal obesity (waist circumference >102 cm in men, >88 cm in women)
- Triglycerides ≥150 mg/dL
- HDL cholesterol <40 mg/dL in men, <50 mg/dL in women
- Blood pressure ≥130/85 mmHg
- Fasting glucose ≥110 mg/dL

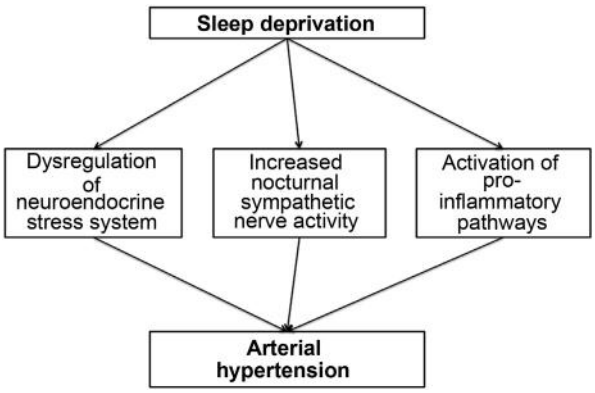

FIGURE 1 Schematic representation of pathophysiological mechanisms linking sleep deprivation and arterial hypertension.

and usually reverted during subsequent recovery sleep. However, chronically restricted sleep not only increases the basal activity of neuroendocrine systems but also may affect the reactivity to subsequent stress exacerbating the basal responsiveness to new stressors (Meerlo et al., 2008).

2. Increased nocturnal sympathetic nerve activity: because SWS has been demonstrated to play a major role in nighttime physiological suppression of catecholamines, a decrease in non-rapid eye movement (NREM) sleep may increase sympathetic nerve activity contributing to the development of arterial hypertension. Experimental SD during REM and NREM has increased nocturnal sympathetic nerve activation, resulting in a nondipping profile and increased blood pressure levels during wakefulness (Sayk et al., 2010).
3. Activation of proinflammatory pathways: SD seems to activate specific inflammatory responses and cytokines (tumor necrosis factor (TNF)-α and interleukin (IL)-1β), resulting in endothelial dysfunction and promoting the progression of arterial hypertension and cardiovascular disease (Sauvet et al., 2010). Precise physiological mechanisms between SD and these immune and inflammatory processes are still unknown.

Partial and total experimental SD has been proved to increase blood pressure in normotensive and hypertensive patients, without any differences in age and sex (Palagini et al., 2013).

Some important cross-sectional studies showed a significant association between sleep loss and hypertension (Kato et al., 2000; Lusardi et al., 1999; Robillard, Lanfranchi, Prince, Filipini, & Carrier, 2011; Tochikubo, Ikeda, Miyajima, & Ishii, 1996). One of these, the Sleep Heart Health Study, reported higher prevalence of arterial hypertension in patients sleeping less than 5 h or more than 9 hours per night compared with those sleeping 7–8 hours per night. The association between SD and hypertension remains significant after adjusting for age, sex, race, body mass index, caffeine and alcohol consumption, and cardiovascular disease. Other studies have provided conflicting results (van den Berg et al., 2007; Fung et al., 2011; Lima-Costa, Peixoto, & Rocha, 2008; Lopez-Garcia et al., 2009). For example, four studies did not find any significant relationship between sleep loss and hypertension in subjects younger than 60 years, after adjustments for confounding factors (Bjorvatn et al., 2007; Hall et al., 2008; Kawada, Okada, & Amezawa, 2008); however, in two of these studies, arterial hypertension was defined as blood pressure ≥135/80 mmHg, according to MS criteria (Hall et al., 2008; Kawada et al., 2008). Moreover, some cross-sectional studies did not show any relationship between sleep loss and hypertension in elderly patients (van den Berg et al., 2007). In fact, the Rotterdam Study did not reveal an association between sleep duration, assessed by self-report or actigraphy, and arterial hypertension in a cohort of 5058 subjects aged 58–98 years (van den Berg et al., 2007). This may be explained by changes in sleep architecture in elderly persons, survival bias, and a paramount role of arteriosclerosis as a causal mechanism of hypertension in older patients.

Two main cross-sectional analyses also showed that association between SD and hypertension might be sex specific (Cappuccio et al., 2007; Stranges et al., 2010). In fact, in the Whitehall II Study, sleeping <5 hours per night was related to higher prevalence of hypertension compared with sleeping 7 hours per night in a subset of women, but not among men (Cappuccio et al., 2007). The Western New York Health Study reported similar data showing a stronger association between sleep loss and hypertension in premenopausal women (Stranges et al., 2010).

Longitudinal studies have reported more convincing evidence regarding the association between sleep loss and hypertension (Gangwisch et al., 2006). The National Health and Nutrition Examination Survey analyzed 4810 adults and showed that subjects sleeping <5 hours per night had higher incidence of arterial hypertension, after adjusting for obesity, diabetes, and other conditions predisposing to hypertension (Gangwisch et al., 2006). In the Chicago Coronary Artery Risk Development in Young Adults Study, SD significantly predicted the development of arterial hypertension over 5 years, after adjusting for main confounding factors (Knutson et al., 2009). Interestingly, in the Outcomes of Sleep Disorders in Older Men Study, the percentage time in SWS, assessed by electroencephalographic recording, was

inversely associated with incident hypertension in the older men, independently by sleep duration and fragmentation; therefore, this study highlights the protective role of SWS sleep and detrimental effects of its selective deprivation (Fung et al., 2011).

In conclusion, most studies support the hypothesis that sleep loss may lead to arterial hypertension; however, causal direction cannot be assessed and the strength of this relationship might be affected by sex and age. In fact, most evidence showed higher risk of developing hypertension in women, in subjects younger than 60 years, and when SWS is mainly decreased.

SLEEP LOSS AND GLUCOSE METABOLISM

Glucose Tolerance during Nocturnal Sleep

During normal sleep, plasma glucose levels remain stable, contrasting with a sharp reduction during fasting in the waking state. During nocturnal sleep, a marked decrease in glucose tolerance with increased plasma glucose levels has been observed (Spiegel, Knutson, Leproult, Tasali, & Van Cauter, 2005). Maximum levels of plasma glucose occur in the middle of the sleep period. During the first part of the night, the increase in plasma glucose is generally followed by a >50% increase in insulin secretion (Spiegel et al., 2005). During this period, decreased glucose tolerance results from a decreased glucose use by peripheral tissues (reduced muscle tone and rapid anti-insulin-like effects of the sleep-onset growth hormone (GH)) (Moller et al., 1990) and mainly by the brain, which showed a 30–40% decrease in cerebral glucose metabolism relative to waking state or REM sleep (Boyle et al., 1994). In the second half of normal sleep, glucose tolerance gradually improves, insulin sensitivity increases, and plasma glucose levels decrease until at morning values, consistent with increase in glucose use. Increased glucose tolerance in the later part of nocturnal sleep is secondary to the increase in wake and REM sleep, which are associated with higher glucose uptake (Scheen, Byrne, Plat, Leproult, & Van Cauter, 1996). Moreover, the interruption in GH secretion and the hypoglycemic activity of previously released insulin also promote the decrease of plasma glucose levels in the later part of nocturnal sleep, increasing insulin sensitivity and glucose peripheral uptake.

Sleep Duration and Glucose Metabolism

Recent evidence shows a significant dysregulation of glucose control in subjects who have decreased sleep times (Spiegel et al., 2005; Spiegel, Leproult, & Van Cauter, 1999; Van Cauter et al., 1991). Moreover, these individuals have been more susceptible to developing metabolic disorders, such as insulin resistance (Spiegel et al., 2005, 1999) and type 2 diabetes mellitus (DM2) (Ayas et al., 2003; Mallon, Broman, & Hetta, 2005; Nilsson, Roost, Engstrom, Hedblad, & Berglund, 2004; Trenell, Marshall, & Rogers, 2007). Pathophysiological mechanisms leading to impaired glucose metabolism in subjects with sleep loss seem to be a decreased efficacy of the negative-feedback regulation of the HPA axis, an impaired regulation in GH, and adipokine secretions.

Sleep Duration and Diabetes Mellitus

Many studies have demonstrated a significant relationship between sleep duration and the development of DM2. Most studies (Ayas et al., 2003; Chaput, Despres, Bouchard, Astrup, & Tremblay, 2009; Trenell et al., 2007; Yaggi, Araujo, & McKinlay, 2006) showed a U-shaped relationship between sleep duration and DM2, reporting that both short (<6 h) and long (>8 h) sleep durations were more likely to develop DM2. This association has been mostly shown in both sexes, although some studies report a stronger relationship in women. However, the lack of association between sleep duration and DM2 in men reported by some studies may be due to the fact that men have higher incidence of obstructive sleep apnea than women, and this SDB may be the paramount reason for their impaired sleep patterns. Testosterone levels may also explain this difference between sexes; in fact, low testosterone levels have been related to insulin resistance and DM2 (Haffner, Karhapaa, Mykkanen, & Laakso, 1994; Pasquali et al., 1997; Stellato, Feldman, Hamdy, Horton, & McKinlay, 2000). Thus, higher levels of testosterone hormone in men might be protective for the development of DM2. Anyway, the differences between sexes have not yet been demonstrated conclusively (Padilha et al., 2011).

SD and Insulin Resistance

Plasma glucose homeostasis results from a balance between glucose delivery (from the gut in the post-prandial state and from the liver in the postabsorptive state) and glucose use (Padilha et al., 2011). Insulin has a paramount role in this tightly controlled balance by inhibiting hepatic glucose production and by stimulating glucose uptake in insulin-sensitive tissues, such as skeletal muscle and adipose tissue, with a final lowering of plasma glucose levels (Padilha et al., 2011; Spiegel et al., 2005). Insulin resistance is defined as a state in which insulin-sensitive tissues have a lowered level of response to insulin. Consequently, pancreatic β-cells produce higher quantities of insulin, but the hyperglycemic state and DM2 develop when β-cell up-regulation becomes unable to maintain normal plasma glucose levels (Padilha et al., 2011; Wilcox 2005).

Spiegel et al. (1999) analyzed glucose metabolism after acute SD (4 hours per night for 6 nights) in 11 young men comparing this sleep-debt condition with measurements taken after a sleep-recovery period (12 hours per night in bed for 6 nights). They reported that glucose effectiveness

(i.e., the ability of glucose to mediate its own disposal independently of insulin) was 30% lower in the sleep-debt condition than after sleep-recovery condition (1.7%/min vs 2.6%/min; $P<0.0005$). This difference was similar to that reported in another study between patients with non–insulin-dependent diabetes and normoglycemic subjects (1.4%/min vs 2.6%/min) (Bergman 1989). Moreover, Spiegel and colleagues also showed that acute insulin response was 30% lower in the sleep-debt condition than in the sleep-recovery condition (304 vs 432 pmol/min; $P<0.04$). Thus, acute total sleep restriction was able to induce important impairment of insulin sensitivity and glucose metabolism. Another study analyzed 27 nonobese patients who were either chronic short sleepers (<6.5 h on weekdays) or normal sleepers (7.5–8.5 hours per night); wrist actigraphy confirmed sleep diaries of patients. Investigators found that short sleepers had normal plasma glucose levels but higher basal C peptide (a marker of insulin secretion) and a 40% reduction in the insulin sensitivity (Mander et al., 2001). This evidence suggests that initial metabolic impairments of glucose tolerance after acute sleep restriction might promote the development of insulin resistance when sleep debt becomes chronic.

Roles of Cortisol and GH in Glucose Metabolism after SD

Cortisol has an inhibitory effect on the secretion of insulin, in absence of changes in plasma glucose levels. After partial and total SD, cortisol levels were significantly increased during the night in young men who had been sleep deprived (Leproult, Copinschi, Buxton, & Van Cauter, 1997). This evidence may be explained by a reduced efficacy of the negative-feedback regulation of the HPA axis (Plat et al., 1999). Moreover, increased activity of the sympathetic nervous system, which results from sleep restriction and subsequent stress situation, may lead to increased cortisol secretion.

GH has an important role in the impairment of glucose regulation after sleep loss. In healthy adults, peak plasma concentrations of GH have been observed in the first half of nocturnal sleep. Immediate anti-insulin-like effects of GH may be responsible for decreased glucose uptake by peripheral tissues and increased insulin resistance observed during the first half of the night. Plat and colleagues reported a longer elevation of GH during the night associated with SD (Plat et al., 1999). In another study, Spiegel and colleagues analyzed the response of GH secretion after semichronic partial sleep loss; GH secretory rates during the sleep-debt condition presented a biphasic pattern of nocturnal release, with a great pulse during waking (before sleep onset), followed by a second pulse after the onset of restricted sleep (Padilha et al., 2011; Spiegel et al., 2000). This biphasic secretory pattern during SD led to higher duration of exposure of peripheral tissue to increased GH levels during sleep times. This extended duration of exposure of peripheral tissues to elevated GH concentrations in sleep-deprived subjects may highly contribute to the dysregulation of glucose metabolism.

Adipokine Changes Associated with SD in the Glucose Metabolism

Adipokines are bioactive peptides and proteins produced by the adipose tissue, including leptin, adiponectin, resistin, and some cytokines (e.g., TNF-α and IL-6). These factors have important roles in the regulation of energy homeostasis and in physiological functions, such as immunity and inflammation (Fantuzzi 2005; Padilha et al., 2011). The release of adipokines by either adipocytes or adipose tissue–infiltrated macrophages has been demonstrated to induce a subinflammatory state that might have a role in the development of impairments in glucose metabolism. In addition, TNF-α, IL-6, and C-reactive proteins have been increased in subjects who are insulin resistant and obese, suggesting a role in the development of DM2 (Antuna-Puente, Feve, Fellahi, & Bastard, 2008). Stress and increased sympathetic nerve activity due to SD may also be a common ground between sleep-debt, adipokine, and insulin resistance (Mullington, Haack, Toth, Serrador, & Meier-Ewert, 2009).

TNF-α is a cytokine produced by macrophages and other cell types and whose expression is up-regulated in adipose tissue of obese and insulin-resistant subjects (Hotamisligil 2000). TNF-α has been deemed to be a molecular link between obesity and insulin resistance (Hotamisligil 2000; Padilha et al., 2011). Several studies showed that TNF-α is able to alter the insulin-signaling pathway in cultured cells in vivo (Mullington et al., 2009), but molecular mechanisms have not been well understood. Adipose tissue TNF-α may lead to insulin resistance by increasing free fatty acid produced by adipocytes, reducing adiponectin synthesis and impairment of insulin signaling (Hotamisligil 2000; Padilha et al., 2011). In humans, TNF-α seems to play a role in sleep homeostasis; the soluble receptor for TNF-α has been a constituent of cerebrospinal fluid and physiologically suppresses sleep. SD affects the TNF-α system, leading to an increase in the overall 24-h TNF-α secretion cycle in men but not in women (Vgontzas et al., 2004).

IL-6 is a proinflammatory cytokine that has a strong correlation with insulin resistance. Plasma levels of IL-6 have been two to three times higher in patients with obesity and DM2 than in lean control subjects (Glund et al., 2007; Padilha et al., 2011).

Leptin is produced by adipocytes in proportion to the total fat tissue and informs the appetite-regulating centers in the hypothalamus about the energy balance, inducing a feeling of satiety. Leptin secretion seems to be stimulated by insulin and promotes fatty acid oxidation, reducing fat accumulation in nonadipose tissues and increasing insulin sensitivity. This effect is directly promoted by leptin by activating AMP-activated protein kinase (AMPK) in skeletal muscles and indirectly through the hypothalamic-sympathetic nervous system

axis (Padilha et al., 2011; Ruderman & Saha, 2006). In fact, leptin directly promotes AMPK activation in skeletal muscles, leading to inhibition of the enzyme acetyl coenzyme A (CoA) carboxylase and decreased levels of intracellular malonyl CoA. This attenuates the inhibition of fatty acid entry into the mitochondria and stimulates fatty acid oxidation. Sleep seems to have a role in promoting leptin production; both chronic and acute SD have been proved to cause decreased serum leptin levels (Mullington et al., 2003; Spiegel, Leproult et al., 2004).

Adiponectin has been demonstrated to have anti-diabetic, anti-atherogenic, and anti-inflammatory functions (Trujillo & Scherer, 2005). Adiponectin increases insulin sensitivity through AMPK activation, like leptin. Adiponectin also alleviates hepatic glucose production by inhibiting phosphoenolpyruvate carboxykinase and glucose-6-phosphatase (Trujillo & Scherer, 2005). Adiponectin seems to reduce the inflammatory response mediated by TNF-α (Trujillo & Scherer, 2005); most inflammatory properties of adiponectin are probably secondary to its anti–TNF-α effects (Maeda et al., 2002). SD causes a reduction in serum adiponectin levels; therefore, this reduction may have a complementary role in the development of insulin resistance in sleep-deprived subjects.

SD AND OBESITY

It is well known that sleep deficiency might play a fundamental role in the development of obesity; in particular, three mechanisms are thought to be responsible, alone or in combination: circadian disruption or chronodisruption, the sleep deficiency, and melatonin suppression. Although it is practical to analyze them individually for academic purposes, they are actually difficult to separate and subsequently overlap and interact.

The circadian rhythm is controlled by neurons located in the suprachiasmatic nuclei (SCN) of the anterobasal hypothalamus; SNC is a biological clock controlling the regular fluctuations of each function in the organism (Garaulet & Madrid, 2009; Green, Takahashi, & Bass, 2008). Melatonin is synthesized mainly during the night (minimally in the daytime) by the pineal gland and has often been referred to as the "chemical expression of darkness" (Reiter 1991). The melatonin cycle provides information about darkness or light to organism cells and then cellular metabolism is based on this information (Reiter 1993). In the past decades, diffusion of artificial lights during the night has altered the sleep/wake rhythm, altering the 24-h melatonin cycle (Duffy & Czeisler, 2009; Jasser, Blask, & Brainard, 2006); this results in suppression of elevated melatonin levels in the nighttime. Light exposure during the night provides incorrect information to SCN about the time of day, and this information is transmitted to other organs; the circadian genes of peripheral cells are regulated by SCN information. Therefore, when this information from the central circadian generator is incorrect, the function of peripheral cells is altered and metabolic disorders may develop. In modern society, some individuals working at night (shift-workers), such as nurses, are easily predisposed to develop chronodisruption (Bass & Takahashi, 2010).

Chronodisruption

Some genes in the adipose tissue (7–21%) are regulated by a circadian rhythm and fluctuate periodically during the entire day; such genes affect the timing of food intake and subsequently fat deposition in the body through the production of several proteins (e.g., adiponectin, resistin, and leptin) and also influence other genes in adipose tissue (Wozniak, Gee, Wachtel, & Frezza, 2009). There are also multiple hormones from the gut, such as ghrelin, which affect food consumption and metabolic activity (Zac-Varghese, Tan, & Bloom, 2010). Therefore, impairments of the central circadian rhythm generator (SCN) have a great impact on the adipocytic genetic system.

Chronodisruption includes both central and peripheral desynchronization of circadian rhythm, resulting in a dysregulation of gene expression in human adipose tissue. Prolonged sleep disturbances may lead to a persistent dysregulation of the neuroendocrine system, which regulates food intake, and lipidic metabolism, which develops into sustained metabolic disorders. For example, Karlsson, Knutson, and Lindhl (2001) analyzed, in a large population-based study of 27,485 subjects, the relationship between shift-work and MS; they found that shift-workers had a higher incidence of abdominal obesity and other components of MS (dyslipidemia, diabetes, and cardiovascular disease).

Some evidence has demonstrated a close dependence of metabolism on the circadian system (Garaulet & Madrid, 2009; Kohsaka & Bass, 2007). Several hormones having a circadian rhythm (e.g., insulin, cortisol, glucagon, and GH) are involved in the control of glucid and lipidic metabolism. Interestingly, Fonken and coworkers analyzed mice after light exposure at night and found that chronodisruption and suppressed levels of melatonin led to altered timing of food intake with preserved total amount of food eaten causing a weight gain (Fonken et al., 2010). However, specific metabolic impairments occurring after SD have not been well identified. Turek et al. (2005) have found that the expression of the CLOCK transcription factor in the SCN might be involved in the development of obesity and MS; the authors reported that CLOCK mutant mice presented several metabolic impairments, such as obesity, hyperlipidemia, hyperglycemia, and hyperinsulinemia. These findings were confirmed by the work of Karatsoreos, Bhagat, Bloss, Morrison, and McEwen (2011), which studied wild-type mice after light exposure during the night and found the same metabolic alterations, suggesting that the environment plays a main role for the development of described metabolic changes. Scheer, Hilton, Mantzoros, and Shea (2009) also showed that chronic and intermittently repeated short-term events of chronodisruption were able to induce considerable metabolic changes in healthy adults.

Sleep Deficiency

Several studies have demonstrated a strong relationship between SD prevalence of obesity and SD, and short sleep times seem to contribute to weight gain in both children and adults (Van Cauter & Knutson, 2008). Decreased sleep times influence energy balance in three ways: appetite up-regulation, increased time and/or frequency of eating, and a reduction in energy expenditure (Van Cauter & Knutson, 2008). Increased body mass may also lead to insulin resistance, which promotes further fat deposition.

Two studies (Chin-Chance, Polonsky, & Schoeller, 2000; Spiegel et al., 1999) reported decreased leptin levels and increased hunger in young men after recurrent partial SD, suggesting that sleep loss decreased the feeling of satiety and led to additional food consumption. Sleep loss was also associated with reduced insulin sensitivity, which increases hunger, food intake, and subsequent weight gain (Van Cauter & Knutson, 2008).

Another experimental study (Spiegel, Tasali et al., 2004) showed that ghrelin, a hormone that stimulates appetite, increased after SD, resulting in a major imbalance of the ghrelin/leptin ratio, which was significantly associated with elevated hunger rating. Therefore, a reduction in leptin levels and an increase in ghrelin production finally led to greater food intake; notably, sleep loss mainly promotes carbohydrate-rich food intake.

Melatonin Suppression

During the night, the pineal gland synthesizes melatonin, which has been proved to have anti-obesity effects (Tan, Manchester, Fuentes-Broto, Paredes, & Reiter, 2011). In humans, the duration of elevated melatonin is proportional to the length of the daily period of darkness (Reiter, Tan, Korkmaz, & Ma, 2012; Wehr 1996); melatonin production is essentially regulated by light exposure (inhibition) and darkness (production). Currently, humans are more exposed to artificial light and, for this reason, they may be considered relatively melatonin deficient, compared with their pre-artificial light counterparts; acute light exposure during the dark period is followed by a quick decrease in melatonin production and in circulating melatonin levels (Lewy, Wehr, Goodwin, Newsome, & Markey, 1980; Rea, Bullough, & Figueiro, 2001). Only darkness is needed for melatonin production; being asleep is not a requirement for elevated melatonin production. Although melatonin promotes sleep, sleep itself is not a requirement for its production. Melatonin has anti-obesity effects irrespective of caloric intake. In fact, some studies have demonstrated that melatonin promotes the growth and metabolic activity of brown adipose tissue, which is widely located in the trunk of humans (particularly in the cervical and thoracic regions), contributing to weight loss (Heldmaier & Hoffmann, 1974; Puig-Domingo, Guerrero, Menendez-Pelaez, & Reiter, 1989; Sinnamon & Pivorun, 1981; Viswanathan, Hissa, & George, 1986).

CONCLUSIONS

Increasing evidence shows that SD may represent a risk factor for components of MS and, consequently, may predispose to cardiovascular disease. A recent meta-analysis confirms that short sleep duration is a risky behavior for increasing the risk of MS and, thus, has important public health implications. Chronic recurrent SD has been proved to induce metabolic and neuroendocrine impairments, leading to obesity, insulin resistance and DM2, and arterial hypertension. Pathophysiological mechanisms leading to these metabolic disorders are complex and mutually interact over time, and they have not been completely understood; further prospective and randomized studies are needed to evaluate all pathophysiological links between SD and MS. Although the evidence about detrimental effects of sleep loss has increased in the past decades, SD is underestimated as a potential risk factor for cardiovascular disorders. For this reason, SD should be considered as a pathological behavior that has to be eradicated.

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Chapter 21

Excessive Daytime Sleepiness: Age, Sleep, Mood, and Metabolic Modulation

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INTRODUCTION

Excessive daytime sleepiness (EDS) is a highly prevalent complaint associated with significant negative effects on health, workplace and academic performance, absenteeism, and overall health and safety, such as motor vehicle collisions (Blachier et al., 2012; Jaussent et al., 2012; Jaussent et al., 2013; Ohayon, 2008; Ohayon, 2012; Strohl et al., 2013). Furthermore, EDS represents a substantial cost burden to the health care system (Jennum & Kjellberg, 2010; Kapur et al., 2002). In clinical practice, EDS is not only the cardinal symptom for the diagnosis of disorders of central nervous system origin such as narcolepsy or idiopathic hypersomnia (American Academy of Sleep Medicine, 2005), but it is the most frequent complaint reported in sleep disorders centers (Roehrs, Carskadon, Dement, & Roth, 2011; Vgontzas & Kales, 1999). Epidemiological studies have shown that the prevalence of EDS ranges between 4 and 20%, depending on the methods and definitions used (Ohayon, 2008). These studies have also shown that the prevalence of EDS is strongly modulated by age, being highest in children, adolescents, and young adults (10–15%), decreasing during middle age (about 6%), and peaking again in the elderly (Bixler et al., 2005; Calhoun et al., 2011; Millman, 2005; Vela-Bueno, Fernandez-Mendoza, & Olavarrieta-Bernardino, 2009). Figure 1 shows this age modulation of the prevalence of EDS in the general population from young age to older adulthood (Bixler et al., 2005).

In this chapter, we will review the multifactorial modulation of EDS. First, we will clarify the definitions used. Second, we will explore each of the most researched factors etiologically linked to EDS. Third, we will explore how each potential factor associated with EDS may be modulated by age within each section. Although narcolepsy and idiopathic hypersomnia are important disorders that should not be neglected (Dauvilliers, Lopez, Ohayon, & Bayard, 2013), this chapter focuses on the modulation of EDS by highly common sleep, mood, and metabolic factors.

DEFINITION

Unlike insomnia, which is a disorder, EDS is a symptom of sleep, mental, or physical health disorders. It is frequently an indication of the degree to which a sleep disorder or another medical problem is negatively affecting the person's daytime functioning. However, similarly to insomnia before a consensus was reached (National Institutes of Health, 2005), EDS has been mislabeled and its findings misrepresented because of a lack of a standardized definition (Ohayon, Dauvilliers, & Reynolds, 2012). For example, epidemiological studies have used different self-reported criteria (e.g., frequency, duration, or severity) or number of questions (e.g., one, two, or an entire scale) to estimate its prevalence (Ohayon, 2008).

Definitions of EDS based on self-reports typically use either two items referring to feelings of sleepiness/tiredness

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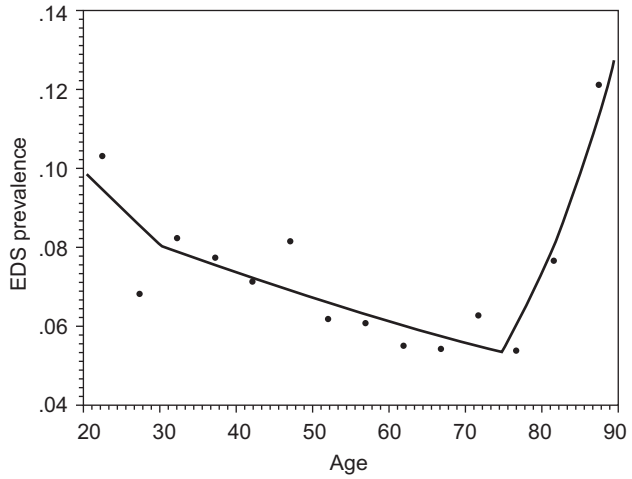

FIGURE 1 Modulation by age of the prevalence of EDS in adults. The prevalence of EDS is highest in young adults, decreases during middle age, and peaks again in the elderly. EDS in the young more likely reflects unmet sleep needs and/or depression, while in the elderly EDS is more likely associated with increasing medical illnesses and health issues. Middle age is a key period in which EDS is modulated by sleep, mood, and metabolic factors. *With permission from Bixler et al. (2005).*

and/or irresistible sleep attacks during the day or a standardized questionnaire, such as the Epworth Sleepiness Scale (ESS). The ESS aims at capturing "sleep propensity," or the probability of falling asleep in specific situations, which is an essential characteristic that distinguishes sleepiness from fatigue (see below). A score greater than 10 on the ESS is indicative of EDS in adults (Johns, 1991). However, most subjective definitions of EDS merge the two constructs and lack discriminant validity between EDS and fatigue. Another term used to refer to EDS is hypersomnia, particularly in the mood disorder literature. Although these two terms may be equivalent, hypersomnia typically implies the presence not only of EDS but also of increased nighttime sleep duration (American Psychiatric Association, 2013). Furthermore, manifestations of EDS in children are often different when compared to adults, especially in young children. For example, sleepy children can experience not only lapses in attention and concentration or difficulty staying on task, but fidgety or hyperactive behavior and irritability (Calhoun et al., 2012; Fallone, Owens, & Deane, 2002; Mayes, Calhoun, Bixler, & Vgontzas, 2009a; Millman, 2005; Owens, 2008). Nevertheless, subjective definitions in children are typically based on parent or teacher observed behavior and are more likely to grasp the sleep propensity component of EDS (i.e., the child is observed to fall asleep in the car, at school, watching TV, etc., vs a report to the parent of tiredness). Thus, from a self-report perspective, EDS should be distinguished from fatigue; however, disentangling the two constructs is rather difficult.

From a physiological perspective, the Multiple Sleep Latency Test (MSLT) is the criterion standard for the objective assessment of sleep propensity (Carskadon et al., 1986). After a nighttime polysomnographic study (PSG), the individual remains in the sleep laboratory to take five 20-min daytime naps that are each 2 h apart. The individual lies in bed in the room with adequate opportunity to sleep (i.e., a dark and quiet room without interruptions) and is asked to try to fall asleep (Roehrs & Roth, 1992). An average MSLT of less than 8 min is considered pathologic and less than 5 min is severely pathologic (American Academy of Sleep Medicine, 2005; Dauvilliers et al., 2013). However, the subjective complaint of EDS correlates weakly with objective findings on the MSLT; for example, the correlation between the ESS and MSLT is at best modest (i.e., $r \sim -0.30$; Aurora, Caffo, Crainiceanu, & Punjabi, 2011). Nevertheless, the MSLT allows the measurement of physiological sleep propensity and helps in disentangling fatigue from EDS. Based on the findings from subjective and physiological studies, Vgontzas et al. (2002) and Vgontzas and Chrousos (2002) defined EDS as "a subjective feeling of physical and mental tiredness associated with increased sleep propensity" and fatigue as "a subjective feeling of physical and/or mental tiredness not associated with increased sleep propensity." These definitions and the differentiation of EDS from fatigue as clinical criteria have been adopted by the insomnia research field (Buysee, Ancoli-Israel, Edinger, Lichstein, & Morin, 2006).

SLEEP

EDS is commonly assumed by physicians and lay persons alike to be the result of insufficient sleep. However, although several studies have shown that fatigue and EDS are frequent manifestations of insufficient or disturbed sleep as a consequence of sleep disorders, many studies have suggested that this association is not as strong as commonly believed.

Experimental studies have consistently shown that acute or chronic sleep deprivation leads to a significant increase in sleep propensity the next day (Durmer & Dinges, 2005). Even a modest amount of sleep restriction (e.g., reducing sleep from 8 to 6 h of sleep per night for 1 week) can increase physiological sleep propensity (Van Dongen, Hans, Maislin, Mullington, & Dinges, 2003; Vgontzas et al., 2004). However, in epidemiological studies, while self-report estimates of habitual sleep duration are independently associated with EDS (Bixler et al., 2005; Punjabi, Bandeen-Roche, & Young, 2003), nighttime sleep duration as measured objectively with PSG is not a significant predictor of EDS. For example, individuals with a complaint of EDS do not necessarily sleep objectively shorter than those without such a complaint (Bixler et al., 2005)—a finding that has been replicated in children from the general population. Calhoun et al. (2011) reported an association between

parent-reported EDS and sleep difficulties; that is, the child is perceived to have trouble falling or staying asleep, but not when PSG markers of sleep duration or disruption were analyzed (e.g., total sleep time, sleep latency, number of long awakenings, number of arousals). This indicates that, as in adults, subjective reports of fatigue or EDS are associated with subjective estimates of nighttime sleep duration or sleep difficulties but do not necessarily reflect insufficient physiological sleep.

It is important, however, to consider that some individuals, particularly adolescents and young adults, may have unmet sleep needs (Bixler et al., 2005; Pallesen et al., 2011) and may fulfill diagnostic criteria for behaviorally induced insufficient sleep syndrome—that is, a complaint of EDS lasting at least 3 months, a shorter than expected habitual main sleep episode, and extended sleep when the habitual sleep schedule is not anchored, such as during weekends or holidays (American Academy of Sleep Medicine, 2005). The prevalence of this syndrome in the general population remains unknown; it may only represent about 7% of patients with a complaint of EDS (Pallesen et al., 2011), and it may be strongly associated with depression, particularly in the young (Komada et al., 2008; Pallesen, et al., 2007). Taken together, these data indicate that the increased prevalence of the complaint of EDS in the young may reflect unmet sleep needs and/or depression (Bixler et al., 2005).

As mentioned, EDS is one of the criteria for daytime functioning impairment for the diagnosis of several sleep disorders, including insomnia (American Academy Sleep Medicine, 2005; American Psychiatric Association, 2013). Individuals with chronic insomnia present with complaints of sleep difficulty for several months and often for years, as well as with daytime functioning complaints such as problems with cognition, energy, and mood. Notable among these daytime complaints are fatigue or exhaustion during the day; however, most individuals with chronic insomnia do not report EDS. In other words, individuals with chronic insomnia report the inability to sleep during the day despite having an opportunity (e.g., a nap) but feeling excessively tired or fatigued (Fernandez-Mendoza, Rodriguez-Muñoz, et al., 2012; Fernandez-Mendoza et al., 2009; Singareddy, Bixler, & Vgontzas, 2010; Vgontzas et al., 2002). These reports have been further supported by data from physiological studies using the MSLT. Mean sleep latency during MSLT has been consistently found to be increased in insomniacs compared to normal controls (Bonnet & Arand, 1995; Edinger et al., 2003; Roehrs, Randall, Harris, Maan, & Roth, 2011; Stepanski, Zorick, Roehers, Young, & Roth, 1988). Furthermore, these studies have shown that the shorter the sleep duration in the PSG the longer the MSLT sleep latency in individuals with chronic insomnia (Bonnet & Arand, 1995; Edinger et al., 2003; Roehrs, Randall, et al., 2011; Stepanski et al., 1988), indicating less sleep propensity (i.e., greater physiological arousal) in those insomniacs with shorter objective sleep duration (Vgontzas, Fernandez-Mendoza, Liao, & Bixler, 2013). When individuals with chronic complaints of insomnia symptoms and daytime fatigue also report EDS (i.e., daytime sleep propensity), it is typically found that such individuals have an underlying primary sleep disorder (e.g., periodic limb movement disorder (PLMD) and/or restless legs syndrome (RLS)) or a disorder of EDS of central origin, such as idiopathic hypersomnia (American Academy of Sleep Medicine, 2005).

Special attention should be given to sleep disordered breathing (SDB), which includes obstructive sleep apnea syndrome. Although EDS is considered the cardinal symptom of SDB (American Academy of Sleep Medicine, 2005; American Psychiatric Association, 2013), their association is rather weak. For example, in clinical samples many patients who present without EDS are found to have a high number of apneas; this is even more frequent in individuals from the general population. For example, the Wisconsin Sleep Cohort, the Sleep Heart Health Study, and the Penn State Adult Cohort have reported that only 16–22% of individuals found to have SDB report EDS (Bixler, Vgontzas, Ten Have, Tyson, & Kales, 1998; Bixler et al., 2001; Kapur, Baldwin, Resnick, Gottlieb, & Nieto, 2005; Young et al., 1993). Finally, the apnea/hypopnea index, a marker of SDB severity, has been found to be weakly associated with the complaint of EDS in both adults and children from the general population in the Penn State Adult Cohort (Bixler et al., 2005) and the Penn State Child Cohort (Calhoun et al., 2011). These data suggest that the number of apneas or sleep disruption are not the primary determinants of EDS in individuals with SDB and that other factors, such as mood, physical activity, or metabolism may play a significant role, even in children (Basta et al., 2008; Bixler et al., 2005; Calhoun et al., 2011; Roure et al., 2008; Tsaoussoglou et al., 2010).

In summary, although self-induced sleep restriction does increase daytime sleep propensity in healthy individuals, its role in the etiology of EDS might be of lesser magnitude when one considers other factors such as depression, physical activity, obesity, and other metabolic factors.

MOOD

In clinical practice, it has been long recognized that many individuals with mood disorders, particularly depression, present with complaints of EDS, irrespective of age (American Psychiatric Association, 2013). For example, a study by Mayes, Calhoun, et al. (2009b) showed that parents of children with a clinical diagnosis of anxiety or depression disorder reported EDS in their children more often than parents of children with attention-deficit/hyperactivity disorder, autism, brain injury, or healthy controls. In fact, epidemiological studies have consistently shown

that depression is one of the strongest risk factors associated with EDS both in children and adults from the general population (Bixler et al., 2005; Calhoun et al., 2011; Hasler et al., 2005; Ohayon et al., 2012; Theorell-Haglöw, Lindberg, & Janson, 2006). However, based only on self-reports, it is not possible to ascertain whether complaints of EDS in individuals with mood disorders reflect fatigue or physiological sleep propensity.

Studies using PSG and MSLT in adults with mood disorders have not found differences in terms of increased nighttime sleep duration or daytime sleep propensity (i.e., shorter average MSLT sleep latency) in individuals with mood disorders as compared to controls (Billiard, Partinen, Roth, & Shapiro, 1994; Dauvilliers et al., 2013; Dolenc, Besset, & Billiard, 1996; Nofzinger et al., 1991; Vgontzas, Bixler, Kales, Criley, & Vela-Bueno, 2000). For example, individuals with psychiatric hypersomnia report severe complaints of EDS but show lower nighttime and daytime sleep propensity (e.g., higher PSG total wake time and longer MSLT sleep latency), while individuals with idiopathic hypersomnia report severe complaints of EDS and show increased nighttime and daytime sleep propensity (i.e., lower PSG total wake time and shorter MSLT sleep latency) than healthy controls (Vgontzas, Papanicolaou, et al., 2000). Preliminary findings from a longitudinal study of the general population suggest that indeed individuals with depression who have PSG sleep disturbances are more likely to develop a complaint of EDS; in individuals without depression, those who show increased PSG sleep propensity (i.e., sleep latency of less than 8 minutes) are more likely to develop a complaint of EDS (Fernandez-Mendoza, Vgontzas, et al., 2012). Taken together, these findings suggest that there is no objective support that individuals with mood disorders have either increased nighttime sleep duration on PSG or sleep propensity on MSLT (Dauvilliers et al., 2013).

In summary, there appears to be a direct association between mood disorders and the complaint of EDS. However, objective studies indicate that most individual with mood disorders who complain of EDS do not show increased physiological sleep propensity. Thus, these individuals are more likely to have sleep disturbances associated with daytime fatigue rather than EDS (i.e., physiological sleep propensity).

METABOLISM

Obesity has increased fourfold in the United States over the past decade and is increasingly recognized as a risk factor for a number of disorders (Flegal, Carroll, Ogden, & Johnson, 2002). Obesity is a well-known risk factor for SDB in both children and adults (Bixler et al., 1998; Bixler et al., 2001; Bixler et al., 2009; Young et al., 1993). Although middle-aged men are more likely to have SDB, women with polycystic ovary syndrome (PCOS) have a much higher prevalence of SDB and EDS as compared to women without PCOS (Fogel et al., 2001; Tasali, Van Cauter, & Ehrmann, 2006; Vgontzas, Legro, et al. 2001). These findings led to the suggestion that EDS in individuals with obesity or metabolic disorders was the result of SDB; however, as we have reviewed above, the association between markers of SDB severity with EDS is not strong and other mediators may be playing a role.

There is evidence for an independent association between obesity and other metabolic aberrations with EDS (Panossian & Veasey, 2012; Punjabi et al., 1999; Resta et al., 2001; Resta et al., 2003; Vgontzas et al., 1998). Epidemiological and clinical studies in both children and adults have confirmed that obesity, as measured by either body mass index (BMI) or waist circumference, is a strong predictor of the complaint of EDS (Bixler et al., 2005; Calhoun et al., 2011; Resnick, Carter, Aloia, & Phillips, 2006; Theorell-Haglow et al., 2006; Tsaoussoglou et al., 2010). Bixler et al. (2005) showed that the BMI-specific prevalence of EDS remained constant until the overweight threshold (BMI = 28) was reached; beyond that BMI threshold, the prevalence of EDS increased in an exponential manner. Multivariate analyses in this study showed that BMI was independently associated with EDS, with an effect size second only to depression. Similar findings have been reported in children from the general population (Calhoun et al., 2011). Furthermore, longitudinal studies have shown that obesity is indeed a strong significant predictor of incident EDS (Fernandez-Mendoza, Vgontzas, et al., 2012), while EDS is not a significant predictor of incident obesity (Vgontzas, et al., 2014), which suggests a causal link between obesity and EDS.

Another factor tightly linked to obesity that has shown an independent association with fatigue and EDS is physical activity. Epidemiological studies have shown that insufficient physical activity is independently associated with feelings of tiredness, exhaustion, or fatigue (Resnick et al., 2006; Theorell-Haglow et al., 2006). In obese men with SDB, regular physical activity has also been shown to be independently associated with lower scores on the ESS (Basta et al., 2008). These combined results suggest that lack of physical exercise is a significant predictor of EDS and fatigue both in clinical and general population samples. However, studies examining the association of physical activity with physiological sleep propensity are lacking.

About 20 years ago, Feinberg (1993) alerted sleep specialists to the possibility that untreated diabetes should be considered in patients with EDS for which other causes had been ruled out. Later, experimental studies showed that sleep deprivation in young healthy adults not only induced EDS but also promoted insulin resistance and impaired glucose tolerance (Spiegel, Leproult, & Van Cauter, 1999). Also, cross-sectional and longitudinal epidemiologic studies in adults have shown that diabetes is a strong independent risk factor for EDS (Bixler et al., 2005; Fernandez-Mendoza,

Vgontzas, et al., 2012). Furthermore, several studies have found that increased insulin resistance and/or fasting glucose levels are significantly associated with EDS in women with PCOS (Tasali et al., 2006; Vgontzas, Legro, et al., 2001), men with SDB (Barceló et al., 2008; Nena et al., 2012), and morbidly obese individuals (Dixon, Dixon, Anderson, Schachter, & O'Brien, 2007). Collectively, these studies suggest that insulin resistance may play a significant role in EDS, even in the absence of SDB or obesity.

Finally, studies have shown that diet is associated with EDS in adults (Panossian & Veasey, 2012). For example, regular high-fat or high-caloric dietary intake has been found to be associated with EDS in women (Grandner, Kripke, Naidoo, & Langer, 2010). A preliminary study showed that high-fat dietary intake had acute effects on physiological sleep propensity as measured with the MSLT (Kritikou et al., 2013). It is possible that cholecystokinin activation may play a role in the association of high-caloric or high-fat diets with EDS (Panossian & Veasey, 2012). Studies using experimental sleep deprivation in sleep disorders have found, although inconsistently, an association of such conditions with impairment in appetite-regulating hormones, such as leptin and ghrelin (Panossian & Veasey, 2012; Pejovic et al., 2010; St-Onge, 2013; Tsaoussoglou et al., 2010). There is a lack of evidence demonstrating a direct independent association between these hormones and EDS.

Similarly to the lack of association between psychiatric hypersomnia and physiological sleep propensity (Vgontzas, Bixler, et al., 2000), the association of obesity with fatigue and EDS is not as simple as it appears. In individuals with obesity, depression or emotional distress is associated with decreased/disturbed sleep and fatigue, whereas the absence of emotional distress in individuals with obesity is associated with increased nighttime sleep and EDS (Vgontzas, Bixler, & Chrousos, 2006). In fact, several studies have shown that in obese individuals, those who sleep objectively longer are also physiologically sleepier during the day (Vgontzas et al., 1998; Punjabi et al., 1999), while no correlation is found between objective measures of nighttime sleep and subjective sleepiness (Resta et al., 2003). Based on these findings, Vgontzas, Bixler, Chrousos, and Pejovic (2008) proposed that emotional distress is the key factor leading to decreased/disturbed sleep and fatigue in some individuals with obesity; in individuals with obesity with increased nighttime sleep and EDS, metabolic (e.g., insulin resistance) and inflammatory disturbances may play a primary mediating role.

There is evidence that the pro-inflammatory cytokines tumor necrosis factor alpha (TNFα), interleukin-1 beta (IL-1β), and interleukin-6 (IL-6) are involved in physiological sleep regulation and that their increased secretion or exogenous administration to humans is associated with fatigue and EDS (Bauer et al., 1994; Gudewill et al., 1992; Kapas et al., 1992; Mastorakos, Chrousos, & Weber, 1993; Opp, 2005; Sothern et al., 1995; Vgontzas et al., 1997; Vgontzas et al., 1999). Experimental sleep deprivation in healthy individuals increases the levels of these cytokines (Vgontzas & Kales, 1999; Vgontzas et al., 2004). Several studies on disorders of EDS in children and adults have reported that both TNFα or IL-6 plasma concentrations are positively correlated with EDS (Gozal & Kheirandish-Gozal, 2009; Patel, White, Malhotra, Stanchina, & Ayas, 2003; Ryan, Taylor, & McNicholas, 2005; Tsaoussoglou et al., 2010; Vgontzas et al., 1997; Vgontzas et al., 2004). Together, these studies suggest that TNFα and IL-6 may play a significant role in mediating EDS. However, studies in sleep disorders associated with disturbed sleep and fatigue but not with physiological sleep propensity, such as insomnia or depression, have shown that in addition to the elevation of pro-inflammatory cytokines, there is a significant activation of the hypothalamic–pituitary–adrenal (HPA) axis in these disorders (Vgontzas & Chrousos, 2002; Vgontzas, Bixler, et al., 2001; Vgontzas et al., 2002; Vgontzas et al., 2003). Thus, it appears that it is the interaction between the stress and immune systems that is the determining factor differentiating disturbed sleep with fatigue from EDS (i.e., physiological sleep propensity).

Such a model serves as the basis to understand the complex association of obesity with EDS and fatigue. Although elevations in pro-inflammatory cytokines have been consistently associated with obesity, some studies have shown hyperactivity of the HPA axis in individuals with obesity (Bjorntorp, 1997; Chrousos & Gold, 1998; Marin et al., 1992; Pasquali et al., 1993; Rosmond, Dallman, & Bjorntorp, 1998), while others have not (Vicennati & Pasquali, 2000; Vgontzas et al., 2008). It appears that hyperactivity of the HPA axis in individuals with obesity may be related to the presence of depression, a condition whose association with HPA axis abnormalities is well established (Chrousos, 2000). These data suggest that individuals with obesity and depression/emotional distress are likely to have disturbed sleep and fatigue, which are mediated by increased pro-inflammatory cytokines coupled with increased activity of the HPA axis; individuals with obesity without depression/emotional distress are likely to have increased nighttime and daytime sleep propensity (i.e., EDS), which is mediated by increased pro-inflammatory cytokines coupled with normal or low activity of the HPA axis (Vgontzas et al., 2008). In a similar vein, this model can also be used to argue that individuals with mood disorders complain of sleep disturbances and fatigue as a result of the same mediating mechanism—the interaction between increased pro-inflammatory cytokines and activation of the stress system (Vgontzas et al., 1997; Vgontzas, Papanicolaou, et al., 2000).

In summary, these data challenge the commonly held belief that insufficient sleep per se is the primary determinant of EDS. It appears that depression, obesity, conditions

of insufficient physical activity, or conditions associated with insulin resistance, such as diabetes and PCOS, are independently associated with fatigue and EDS. In fact, within individuals with obesity, those who sleep longer at night are physiologically sleepier during the day than those who have sleep disturbances. Thus, it appears that EDS is primarily related to metabolic and inflammatory factors, whereas fatigue appears to be more related to emotional distress (i.e., depression). The interaction between the stress and immune systems appears to determine the level of arousal within the 24-h cycle: Increased activity of the stress system coupled with low-grade inflammation is associated with decreased/disturbed sleep and fatigue, whereas normal or decreased activity of the stress system coupled with low-grade inflammation is associated with increased sleep and EDS.

PUBLIC HEALTH AND CLINICAL IMPLICATIONS

EDS is a highly prevalent complaint in both children and adults. It takes a toll on many key indicators of public health: mortality, morbidity, performance, accidents and injuries, quality of life, and family well-being, and it represents a substantial cost burden to the health care system. From a public health perspective, an important finding in the reviewed literature is the link between EDS and widespread factors of almost epidemic proportions, such as obesity, depression, physical inactivity, and diabetes and other disorders of insulin resistance. Thus, public health policy in the prevention of the EDS and fatigue should target these well-defined risk factors.

From a clinical standpoint, providers treating individuals with complaints of EDS should screen for more than sleep disorders and insufficient sleep. Clinicians should also aim at disentangling fatigue from EDS. Although PSG is extremely useful in screening children and adults for sleep disorders such as SDB, narcolepsy, or PLMD, clinicians should be cognizant that PSG markers of sleep duration and disruption are not strongly associated with the complaint of EDS. Therefore, differential diagnosis should not only include sleep disorders but also all the potential risk factors reviewed above. Obesity, depression, diabetes, as well as asthma and medication side effects should be considered as contributing factors in the clinical evaluation (Bixler et al., 2005; Calhoun et al., 2011; Ohayon, 2008) and not simply comorbid with these conditions. This same strategy, in which known risk factors are included in the clinical evaluation, should be applied to children referred for a complaint of EDS. In turn, when children are referred for neurobehavioral problems, they should be assessed for EDS. A study in children from the general population demonstrated the potential for EDS to be associated with behavioral morbidity, including inattention/hyperactivity, learning difficulties, and conduct problems such as externalizing behaviors of opposition, rule-breaking, impulsiveness, and explosiveness, through its impact on neurocognitive functioning (Calhoun et al., 2012). This study showed that impaired processing speed and working memory mediated the relationship between the parent-reports of EDS and behavioral problems. Thus, in children with inattention/hyperactivity, learning difficulties, and conduct problems and EDS, assessment of objective neurocognitive weaknesses may be useful in identifying the most severe cases.

Consistent with the broad clinical evaluation proposed, the targeted treatment of EDS should be multifactorial. For example, in children and adults with a complaint of EDS, primary lines of treatment might include weight loss (if the patient is overweight or obese) and treatment for depression and/or anxiety as well as sleep disorders when appropriate. Preliminary longitudinal studies in adults and children have shown that the remission of EDS is associated with weight loss (Calhoun et al., 2013; Fernandez-Mendoza, Vgontzas, et al., 2012). It is possible that the beneficial effect of increasing physical activity on EDS is through improvement of insulin resistance, central adiposity, or pro-inflammatory cytokine levels (Basta et al., 2008; Tsaoussoglou et al., 2010). In children with behavior problems such as externalizing behaviors, inattention, and learning difficulties, the recognition and treatment of EDS can offer new strategies to address some of the most common neurobehavioral challenges in this age group. As depicted in Figure 2, targeting

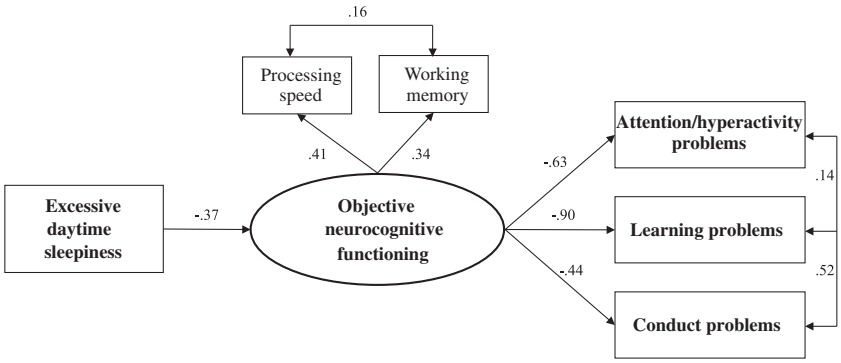

FIGURE 2 Objective neurocognitive functioning mediates the relationship between parent-report of EDS and behavioral problems. EDS slows down the child's thought processes or ability to process information in a quick and efficient manner, which is observed as lower alertness and concentration, and leads to inattention/hyperactivity, learning difficulties, and conduct problems (e.g., irritability, opposition, and aggression). *With permission from Calhoun et al. (2012).*

EDS per se may improve neurocognitive deficits as well as behavioral problems in young children.

In summary, public policy should target EDS. Clinicians should approach EDS from a multifactorial perspective without simply assuming that it is the result of insufficient sleep. Sleep, mood, and metabolic disorders should be part of the differential diagnosis and targeted with treatment when appropriate. Importantly, clinicians should distinguish fatigue from EDS and be cognizant of which conditions and mechanisms are more likely to play a role in each.

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Chapter 22

The Metabolic Role of Saturated and Monounsaturated Dietary Fatty Acids: Their Contribution to Obesity, Brain Activity, and Sleep Behavior

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METABOLIC ABNORMALITIES DURING OBESITY

Over the past 3 decades, insulin resistance-associated conditions such as obesity and type 2 diabetes (T2D) have reached epidemic proportions. Obesity is a well-recognized factor for T2D, and the incidence for obesity is climbing at an alarming rate, underscoring urgency for the discovery of effective therapies to combat this epidemic, particularly because overweight and obesity are the fifth leading risks for death (IDF, 2013). Globally, about 0.5 billion adults are obese, 0.9 billion are overweight, and nearly 0.4 billion have T2D (IDF, 2013). A central cause of overweight and obesity is an energy imbalance between calories consumed and calories expended, and it is proposed that a complex interplay of environmental, including fetal programing and genetic, behavioral, neuronal, and endocrine factors, has a central role in the development of obesity and T2D. Most obese individuals have insulin resistance, T2D, dyslipidemia, and other metabolic complications. However, a subgroup of approximately 10–25% of subjects with obesity preserves insulin sensitivity and is metabolically healthy (Stefan, Häring, Hu, & Schulze, 2013; Stefan et al., 2008). Neither the genetic factors causing healthy obesity nor the causal factors for transition between the healthy and unhealthy obese phenotype are understood in detail. It is accepted that visceral adipose tissue distribution and ectopic fat deposition are key parameters and potential causal factors for the development of insulin resistance independently of total body fat mass (Kirchhoff et al., 2007; Stefan et al., 2008; Wildman, 2009). Thus, it was found that enlarged adipocytes size, gene expression modifications of key adipose tissue genes, macrophage infiltration with impaired adipocytes function, and a dysregulation of circulating adipokines and cytokines are related to insulin-resistant unhealthy obesity (Hardy et al., 2011; Stefan et al., 2013). A growing body of evidence indicates that impaired regulation of metabolic physiology by the central nervous system (CNS) is a characteristic feature of obesity and T2D (Sisley & Sandoval, 2011). To effectively combat the current obesity epidemic, it is urgent to increase our understanding of the complex and neural mechanisms underlying the homeostatic and non-homeostatic control of energy balance (intake and expenditure).

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INSULIN ACTION IN THE BRAIN

Insulin has pleiotropic effects on core physiological functions, such as regulation of glucose homeostasis by promoting glucose uptake in muscle and fat tissue, and by suppressing hepatic glucose production (Könner et al., 2007). The CNS in part regulates these homeostatic mechanisms, because it was demonstrated that centrally administered insulin mediates the antigluconeogenic effect (Könner et al., 2007; Obici, Zhang, Karkanias, & Rossetti, 2002; Pocai et al., 2005). Furthermore, insulin has neuroprotective properties and is involved in the regulation of learning and memory (Plum, Schubert, & Brüning, 2005), but this recently emerging field is not yet fully understood. Likewise, the anorexigenic effect of insulin has been attributed to its action in the arcuate nucleus of the hypothalamus (Elmquist, Coppari, Balthasar, Ichinose, & Lowell, 2005), and insulin signaling specifically in the ventromedial nucleus of the hypothalamus is involved in the onset of obesity upon high-fat diet (HFD) feeding (Klöckener et al., 2011). However, insulin may also act directly on associated neuronal circuitries, because it was shown that energy homeostasis is subject to the control of insulin action in catecholaminergic neurons, apparently via regulation of hedonic feeding circuits (Könner et al., 2011).

BRAIN INSULIN RESISTANCE

Insulin resistance significantly contributes to diabetes development and is strongly linked to obesity, excess ectopic lipid deposition in insulin target tissues, and perturbations in lipid metabolism (Samuel & Shulman, 2012). So far, the exact molecular mechanisms are not yet fully understood, and it is becoming increasingly accepted that the brain is involved in metabolic abnormalities seen in obesity, insulin resistance, and T2D. Similar to animal studies in which insulin sensitivity in the brain is blunted in obese and insulin-resistant mice, the effect of insulin on neuronal activity in humans is impaired in obesity (Tschritter et al., 2006) and aging (Tschritter, Hennige, et al., 2009). Further, functional magnetic resonance imaging (fMRI) studies identified specific brain areas related to object processing, memory, and locomotion in lean and obese subjects. Thus, the hippocampus is known to control brain activity in the theta frequency band, and this frequency range could be correlated to locomotor activity during lifestyle intervention lasting 9 months (Tschritter et al., 2012). Thereby, high insulin sensitivity of the human brain facilitates loss of body weight and body fat by lifestyle intervention.

There is a growing body of evidence demonstrating that one of the prominent progressions toward the onset of neuronal insulin resistance is existing crosstalk between insulin signaling and low-grade inflammation associated with HFD-induced obesity (Sartorius, Lutz, et al., 2012; Thaler, Guyenet, Dorfman, Wisse, & Schwartz, 2013). Many molecular signaling pathways have been described at the interface between inflammation and metabolism (e.g., insulin receptor (IR) signaling). Thus, it was demonstrated that insulin signaling is directly impaired by activation of inflammatory signaling cascades within the brain by elevated saturated fatty acids (SFAs) and/or increased release of obesity-induced proinflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukin 6 (IL-6), and osteopontin (OPN) (Sartorius, Lutz, et al., 2012; Thaler et al., 2013). In detail, inflammatory kinases such as c-Jun N-terminal kinase (JNK) and inhibitor of κB-kinase-β (IKKβ), which activates nuclear factor-κB (NF-κB), are activated and further trigger endoplasmic reticulum (ER) stress, which enhance NF-κB activity (Zhang et al., 2008). Thereby, IR signaling is directly blunted by interference with phosphorylation sites downstream of IR signaling, and JNK activation leads to phosphorylation of insulin receptor substrate 1 at serine-307 residue with impaired insulin action (Aguirre, Uchida, Yenush, Davis, & White, 2000). Interestingly, when these intracellular proinflammatory signals are inhibited, peripheral metabolism and central insulin sensitivity are restored. For instance, this was observed in a study performed in rodents in which peripherally and centrally administered IL-6 antibody ameliorated insulin sensitivity in the brain of HFD-fed mice (Sartorius, Lutz, et al., 2012).

FATTY ACID SIGNALING THROUGH RECEPTORS

One of the hallmarks of obesity is an increase of circulating free fatty acids (FFAs), which act as metabolic sensors in the brain, and intracellular lipid intermediates (such as diacylglycerols and ceramides) are implicated in the pathogenesis of insulin resistance by impairing intracellular key signaling pathways. Signaling mechanisms through surface receptors such as Toll-like receptors (TLRs) are a proposed link by which obesity causes central insulin resistance (see Figure 1). TLRs belong to the pattern recognizing receptors, components of the innate immune system, and have the ability to sense endogenous ligands in the obese state. Among TLRs, TLR2 and TLR4 are expressed in almost all cell types within the brain (Hanisch, Johnson, & Kipnis, 2008), and recent findings demonstrated that TLR2 and TLR4 are a causal link in the progression toward obesity and central insulin resistance (Sartorius, Lutz, et al., 2012; Tsukumo et al., 2007). This is highlighted by the observation that lack of functional TLR2/4 protects mice from SFA-mediated impairment in peripheral and central insulin action, brain activity, locomotion, and sleep architecture by an IL-6/OPN-dependent mechanism (Sartorius, Lutz, et al., 2012). However, current evidence suggests that FFAs do not directly bind to TLR4, but an endogenous ligand for TLR4, fetuin-A, has a crucial role in regulating insulin sensitivity

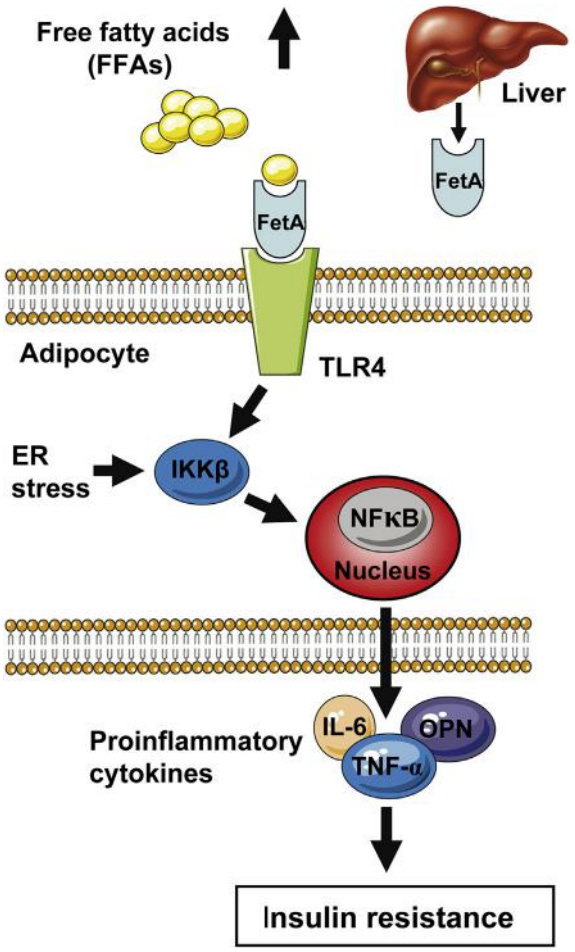

FIGURE 1 Free fatty acids (FFAs) and Toll-like receptor 4 (TLR4) signaling in fat-induced inflammation leading to insulin resistance. FFAs bind to the endogenous ligand for TLR4, fetuin-A, which is produced by the liver. TLR4 signaling induces the activation of the transcription factors nuclear factor κB (NFκB), which results in the production of proinflammatory cytokines leading to insulin resistance. ER, endoplasmic reticulum; IKKβ, inhibitor of NFκB kinase-β; IL-6, interleukin 6; OPN, osteopontin; TNF-α, tumor necrosis factor-α. *Modified after Heinrichsdorff and Olefsky (2012).*

via TLR4 signaling in mice (Pal et al., 2012). Although these results might imply that SFAs are affected by TLR4 activation, a recent study revealed that hepatic insulin resistance is independent of TLR4 signaling and ceramide synthesis (Galbo et al., 2013).

Another cell-surface fatty acid receptor is the free fatty acid receptor 1 (FFAR1) (formerly G protein-coupled receptor 40 (GPR40)), which is activated by physiological concentrations of medium and long chain saturated and unsaturated fatty acids with carbon chain lengths of more than 10 (Briscoe et al., 2003). In humans, FFAR1 is specifically expressed in brain and pancreas, accurately in pancreatic insulin-producing β cells. Some physiological effects of fatty acids in pancreatic islets and brain are mediated through this cell-surface receptor. For instance, an acute increase in FFAs potentiates glucose-induced insulin secretion by activating FFAR1 (Itoh et al., 2003). In vitro experiments further revealed that the SFA palmitate stimulates glucose-induced insulin secretion through FFAR1. The proapoptotic effect of chronic exposure of β cells to palmitate was independent of FFAR1, because inhibition of FFAR1 promoted apoptosis (Wagner et al., 2013). In accordance, animal studies suggested that the deleterious effect of prolonged FFA elevation is independent of FFAR1 activation, because mice deficient in FFAR1 were not protected against HFD-induced glucose intolerance (Lan et al., 2008).

IMPACT OF FAT ON GLUCOSE HOMEOSTASIS

The obesogenic lifestyle, characterized by an increased intake of energy-dense foods that are high in fat, and reduced physical activity, is often the result of environmental and societal change, and the association between lipids and insulin resistance is widely accepted. Per definition, fatty acids are aliphatic monocarboxylic acids derived from or contained in esterified form in an animal or vegetable fat, oil, or wax (IUPAC, 1997). Fatty acids are classified as SFAs and unsaturated fatty acids. The latter have one or more carbon–carbon double bonds and are adequately subdivided into monounsaturated fatty acids (MUFAs) and polyunsaturated fatty acids (PUFAs). MUFAs are highly presented, for example, in canola oil (>63% oleic acid), whereas plant oils such as linseed oil and fish contain high amounts of PUFAs (such as linoleic acid and arachidonic acid). The most important PUFAs for humans are divided into two groups: n-6 and n-3 PUFAs. Western diets are high in n-6 and low in n-3 PUFAs, which is speculated to promote insulin resistance and diabetes; decreasing the dietary n-6/n-3 ratio in T2D patients could improve insulin action (De Caterina, Liao, & Libby, 2000; Raheja, Sadikot, Phatak, & Rao, 1993). There is further evidence of the importance of n-3 PUFAs for brain development during fetal and early postnatal life. For instance, the abundance of n-3 PUFAs in the diet of pregnant females is indispensable for development of the glutamatergic system and normal behavior performance in the adult offspring (Moreira et al., 2010). MUFAs were shown to prevent the deleterious effects of palmitate, an SFA, and glucose on pancreatic β-cell turnover and function (Maedler, Oberholzer, Bucher, Spinas, & Donath, 2003), and MUFAs completely prevented palmitate-induced apoptosis in β cells (Eitel et al., 2002). Insulin secretion was further inhibited by chronically elevated SFAs, which led to an increased rate of apoptotic β cells in the pancreas (Eitel et al., 2003). A study that shaped the concept of an inverse correlation between FFAs and insulin sensitivity was performed in offspring of T2D patients, in whom elevated FFAs represent an early step in the progression toward T2D (Perseghin, Ghosh, Gerow, & Shulman, 1997). The notion that fatty acids can signal nutrient availability to the

CNS, which in turn limits further delivery of nutrients to the circulation, is supported by studies in rodents, in which the centrally administered MUFA oleic acid markedly inhibits glucose production and food intake (Obici, Feng, et al., 2002). Moreover, Lam et al. (2005) demonstrated an important role of hypothalamic sensing of circulating fatty acids in the regulation of glucose homeostasis in response to a physiological increase in lipid availability. Circulating fatty acids are generally bound to albumin and penetrate the blood–brain barrier by simple diffusion in the unbound form. Hydrolysis of lipoproteins by lipoprotein lipase within blood or at the cerebral capillary bed further produces unbound fatty acids. Therefore, in the post-meal state, chylomicrons are presumably a major circulating source of brain fatty acids, whereas in the fasting state the fatty acid pool in the brain is constituted by a combination of unbound fatty acids and locally hydrolyzed lipoproteins. Notably, a direct uptake of lipoproteins by specific receptors in the luminal surface of the cerebrovascular endothelium also accounts for a small portion of fatty acid accretion into the brain (Qi, Hall, & Deckelbaum, 2002). Proportionality exists between the plasma concentration of circulating FFAs and their access to the CNS (Rapoport, 1996), and it was shown several decades ago that in fasted anesthetized dogs the concentration of plasma in cerebrospinal fluid (CSF) is around 6% (Goto & Spitzer, 1971). Interestingly, a recent study in humans revealed a positive relationship between the n-3 PUFA docosapentaenoic acid and docosahexaenoic acid, and the n-6 PUFA arachidonic acid in the blood and the CSF (Guest, Garg, Bilgin, & Grant, 2013). The authors further found an inverse association between central and peripheral oleic acid. With regard to the impact of fatty acids on neuronal function, magnetoencephalography studies in humans revealed that chronically elevated serum levels of SFAs are associated with impaired insulin action in the brain. Therefore, levels of SFAs were negatively correlated with insulin-stimulated brain activity in certain frequency bands, and obese subjects who were characterized by elevated levels of SFAs displayed insulin resistance independently of body weight (Tschritter, Preissl, et al., 2009; Tschritter et al., 2006). Moreover, rodent data suggested that mice challenged with HFD based on lard are characterized by impaired insulin action in the brain and impaired cortical activity and locomotion as assessed by radiotelemetry (Hennige et al., 2009). This might further promote glucose intolerance, physical inactivity, and obesity.

FAT QUALITY CORRELATES WITH INSULIN SENSITIVITY

An emerging body of evidence suggests that dietary fat quality and not its total fat content more closely correlates with alterations in insulin sensitivity and weight gain in humans and animals (Haag & Dippenaar, 2005; Jucker, Cline, Barucci, & Shulman, 1999). Thus, to assess the effects of quality and quantity of several diets high in fat, mice were fed long-term with different concentrations and types of fat (Yu et al., 2010). The analysis of the study implied that these diets not only modified the brain fatty acid composition but also altered spatial memory and learning ability in mice. However, numerous studies demonstrating aversive effects of SFA overload on glucose metabolism were performed in rodents fed high caloric diets consisting of a large amount of fat. However, it remains to be determined whether moderate, isocaloric fat enrichment with diets that differ in fat quality have an impact on glucose homeostasis. This issue was examined in a study in which an SFA-enriched diet was accompanied by glucose intolerance, reduced brain activity, and central insulin resistance in mice, whereas an isocaloric MUFA-enriched diet protected from these deleterious effects (Sartorius, Ketterer, et al., 2012). The MUFA-fed animals gained significantly increased fat mass comparable to the SFA-fed group, but this did not raise concerns about glucose homeostasis.

CONSEQUENCES OF IMPAIRED SLEEP BEHAVIOR ON METABOLISM

Sleep is an important modulator of neuroendocrine function and glucose metabolism, and electroencephalography and electrocorticography recordings are widely used to define sleep stages. A large number of laboratory studies of humans as well as epidemiological data suggest that short sleep duration is associated with metabolic and endocrine alterations, including impaired glucose tolerance, decreased insulin sensitivity, and increased hunger and appetite (Chaput, Després, Bouchard, & Tremblay, 2007; Knutson, Van Cauter, Zee, Liu, & Lauderdale, 2011). Most recent evidence linking decreased nocturnal sleep duration and poor sleep quality to an increased risk of developing obesity and its complications were demonstrated by multiple epidemiological studies in adults and children (Knutson, Van Cauter, 2008; Patel & Hu, 2008; Leproult & Van Cauter, 2010; Lucassen, Rother, & Cizza, 2012; Mathew & Narang, 2013). A significant association between short sleep duration (6 h or less per night) and elevated obesity risk was found in which hormonal alterations favored an increase in caloric intake and decreased energy expenditure, and led to body weight gain. Multiple pathways are prone to mediate the relationship between sleep and obesity. For instance, sleep restriction enhances the food intake-stimulating peptide ghrelin (Spiegel, Tasali, Leproult, Scherberg, & Van Cauter, 2011) and conversely, the satiety-inducing hormone leptin declines (Spiegel et al., 2004). Importantly, the secretion of these two hormones from adipocytes (leptin) and from stomach and pancreas (ghrelin), respectively, is also modulated by the autonomic nervous system, and a shift of the sympathovagal balance to higher sympathetic activity has been observed in sleep deprivation studies (Spiegel et al., 2004). Furthermore, an association

was found for partial sleep loss and disturbance of glucose homeostasis that involves both reduced β-cell responsiveness and lower insulin sensitivity (Van Cauter et al., 2007). Notably, a recent study explored brain regions most susceptible to sleep deprivation-induced changes when processing food stimuli, assessed by fMRI in humans (Benedict et al., 2012). Thus, total sleep deprivation was associated with increased activation in the right anterior cingulate cortex in response to food images, and this was independent of calorie content and plasma glucose levels.

METABOLIC SLEEP DISTURBANCES

Against the background of the previous section it is interesting to assess whether specific fat classes have effects on sleep architecture and to explore the role of different brain areas taking part in regulating sleep behavior mediated by different fat qualities. Sartorius, Ketterer, et al. (2012) showed that mice chronically fed an isocaloric SFA-enriched diet were characterized by decreased wakefulness and increased non-rapid eye movement (NREM) sleep (see Figure 2(A)–(C)). In line with these findings, an intervention study in humans demonstrated that SFA intake deteriorates brain activity in the hippocampus and the inferior parietal cortex, whereas MUFAs did not display averse effects as assessed by fMRI techniques (see Figure 2(D)–(E)) (Sartorius, Ketterer, et al., 2012).

It is known that the lateral and posterior hypothalamic areas contain neurons specifically active during wakefulness (Vanni-Mercier, Sakai, & Jouvet, 1984), and that the medial prefrontal cortex and basal forebrain are counted among wake-promoting regions (Datta & Maclean, 2007). The promising findings of this fat quality study (Sartorius, Ketterer, et al., 2012) suggest that SFAs may specifically act on brain areas controlling wakefulness and NREM sleep, whereas MUFAs preferentially alter mechanisms in the brainstem and especially the pons and adjacent portions of the midbrain, because this fat class predominantly affects rapid eye movement (REM) sleep. So far, however, the underlying molecular mechanisms are unclear and remain to be determined. Further findings suggest an association between n-3 PUFAs and pineal function, which is implicated in the sleep–wake rhythm. Syrian hamsters nourished with an n-3 PUFA-deficient diet are characterized by disturbance in melatonin rhythm, weakened endogenous functioning of the circadian clock, and impaired nocturnal sleep (Lavialle,

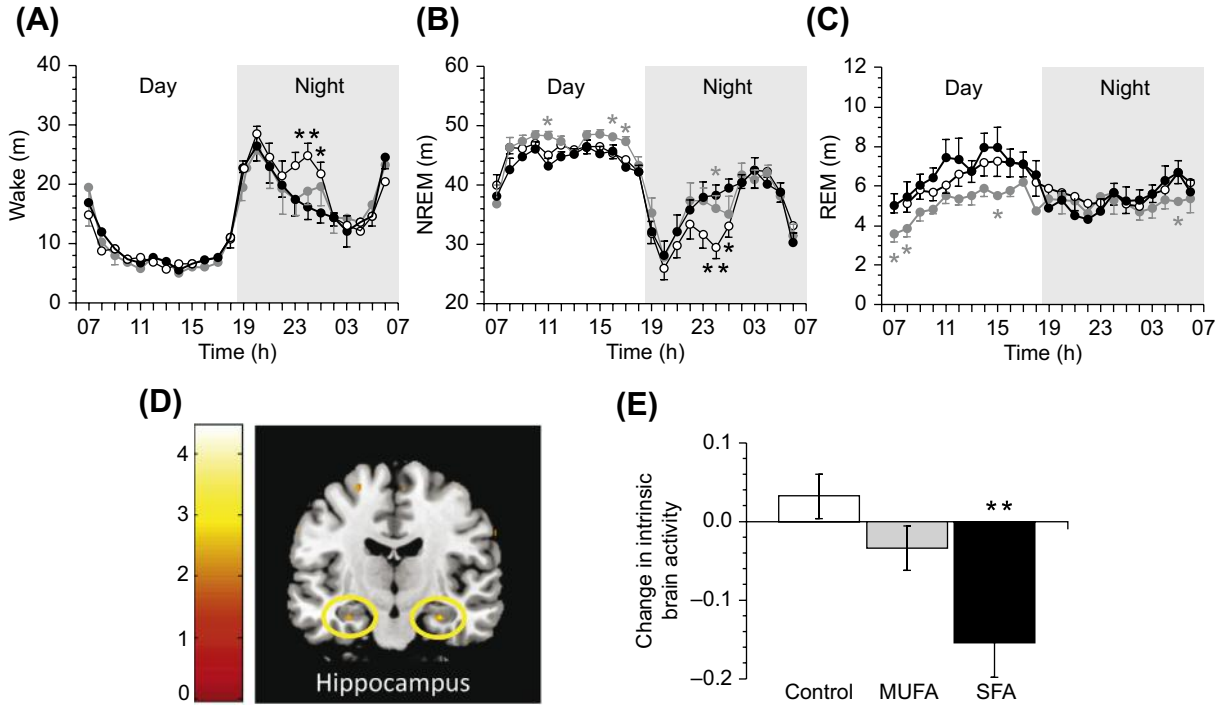

FIGURE 2 Different sleep–wake patterns in monounsaturated fatty acid (MUFA)- and saturated fatty acid (SFA)-fed mice and response of the human brain to MUFA- and SFA-enriched diet. (A–C): Diurnal variations of wakefulness (wake), non-rapid eye movement (NREM) sleep, and rapid eye movement (REM) sleep in MUFAs- (gray circles), SFAs- (black circles), or chow-fed (white circles) mice. Data (mean ± SEM of 11–14 animals/diet group) are expressed as minutes per hour for each hour over a 24-h episode (light on 07:00 AM to 07:00 PM). (D–E): Color-coded T-value map represents significant voxels of decreased intrinsic brain activity 3 months after SFA-enriched yogurt consumption compared with the control group ($p < .001$, whole brain). Plots show change of intrinsic activity in the hippocampus 3 months after SFA-enriched, MUFA-enriched, and control diet. Only SFA-enriched diet revealed a significant decrease in hippocampal activity. Statistically significant differences between fat-enriched diet groups and control group are depicted by asterisks (*$p < .05$; **$p < .005$). Data are presented as mean ± SEM.

Champeil-Potokar, Alessandri, Balasse, & Guesnet, 2008). Likewise, rats deficient in n-3 PUFAs showed dysregulation of monoaminergic systems in the frontal cortex and nucleus accumbens, both of which areas have a central role in the reward circuit (Chalon, 2006).

In general, the obesogenic lifestyle, particularly present in Western society, with an excess uptake of SFAs and, to some extent, n-6 PUFAs, entails negative consequences, whereas MUFAs and n-3 PUFAs are advantageous. Recent research provides new opportunities to understand the pathogenesis of organ-specific diseases associated with obesity and offers new strategies for beneficial and targeted therapy. However, in studies using a nutritional approach, other food ingredients may exert positive or negative effects that may limit the translatability of controlled successful animal studies into therapeutic interventions in humans. Moreover, evidence from multiple sleep and obesity studies supports the importance of sufficient sleep of good quality in subjects at risk for obesity. Finally, sleep is the most sedentary activity and yet may be the only one that protects from weight gain (Chaput, Klingenberg, & Sjodin, 2010).

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Part IV

Sleep and Diabetes

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Chapter 23

Obstructive Sleep Apnea and Diabetic Microvascular Complications

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INTRODUCTION

Type 2 diabetes (T2D) is a global epidemic causing a massive burden on society and the economy. By 2030, it is estimated that 7.7% (438 million) of the world's population will have T2D. Already in 2010, approximately 12% of the world's health budget was spent on diabetes and its related complications (Guariguata et al., 2013).

T2D is a complex disorder in which genetic and environmental interactions result in varying degrees of insulin resistance (IR) and progressive β-cell dysfunction (Stumvoll, Goldstein, & van Haeften, 2005). Failure of the β cells to secrete enough insulin to overcome the IR results in dysglycemia and T2D (Stumvoll et al., 2005). Although several genetic and environmental factors are involved in the pathogenesis of T2D, obesity remains the single most important factor (Kahn, Hull, & Utzschneider, 2006; Stumvoll et al., 2005).

Vascular disease (micro and macro) is a major cause of morbidity and mortality in patients with T2D (Irene et al., 2000; Roberts, 2006). Diabetic microvascular complications include diabetic peripheral neuropathy (DPN), diabetic nephropathy (DN), diabetic retinopathy (DR), and diabetic autonomic neuropathy (DAN). DPN causes foot ulceration and is the leading cause of nontraumatic lower limb amputations (Tahrani, Askwith, & Stevens, 2010; Tahrani, Zheng, et al., 2012). DN is the most common cause of end-stage renal disease, requiring renal replacement therapy and/or renal transplantation (Leiter, 2005). DR is a leading cause of blindness in the Western world and results in significant morbidity and economic burden (Cheung, Mitchell, & Wong, 2010). DAN is associated with increased risk of cardiovascular disease and death (Dimitropoulos, Tahrani, & Stevens, 2014). Hence, reducing the burden of vascular disease is a major aim of treatment in patients with T2D.

Several studies have shown that improvements in glycemic control (The Diabetes Control and Complications Trial Research Group, 1993; Holman, Paul, Bethel, Matthews, & Neil, 2008), blood pressure (Adler et al., 2000; Stratton et al., 2006; UK Prospective Diabetes Study Group, 1998), lipid levels (Davis, Yeap, Davis, & Bruce, 2008; Fried, Orchard, & Kasiske, 2001; Leiter, 2005) and the use of blockers of the renin-angiotensin-aldosterone system (Malik et al., 1998) delay the development or slow the progression of diabetic microvascular complications. However,

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despite these significant improvements, microvascular complications remain very common. Therefore, a better understanding of the pathogenesis of these conditions is needed in order to identify new treatment targets.

Obstructive sleep apnea (OSA) is a common disorder that is highly prevalent in patients with T2D (Tahrani, Ali, & Stevens, 2013). It is characterized by upper airway instability during sleep, resulting in markedly reduced (hypopnea) or absent (apnea) airflow (McNicholas, 2008). These apnea/hypopnea episodes are usually accompanied by cyclical oxygen desaturations and cyclical changes in blood pressure (BP) and heart rate (McNicholas, 2008). Because OSA is associated with many of the pathophysiological deficits that are found in diabetes (Tahrani & Ali, 2014; Tahrani, Ali, et al., 2012; Tahrani, Ali, et al., 2013), it seems reasonable to speculate that OSA could play an important role in the development or progression of diabetic microvascular complications.

In this chapter, we will explore how OSA might be related to diabetic microvascular complications and review the literature examining the presence of such a relationship in clinical studies.

THE PATHOGENESIS OF DIABETIC MICROVASCULAR COMPLICATIONS

The pathogenesis of diabetic microvascular complications is complex and multifactorial (Figure 1). The main driver for the development of these complications is hyperglycemia, which activates several pathways leading to increased inflammations, endothelial dysfunction, and microvascular disease (Figure 1) (Brownlee, 2001; Brownlee, 2005; Tahrani et al., 2010).

Advanced Glycation Endproducts

Advanced glycation endproducts (AGEs) result from the reaction of different di-carbonyls (glyoxal, 3-deoxyglucosone, and methylglyoxal) with amino groups of intracellular and extracellular proteins (Brownlee, 2001). AGEs can modify intracellular proteins involved in endocytosis and the regulation of gene transcription (Brownlee, 2005); bind to the extracellular matrix, resulting in changes in signaling between the matrix and the cell (Brownlee, 2001; Brownlee, 2005); modify circulating proteins such as albumin, which can then bind to receptor of AGE (RAGE), causing increased inflammatory cytokines, growth factors, and adhesion molecules (Abordo & Thornalley, 1997; Brownlee, 2001; Brownlee, 2005; Kirstein, Aston, Hintz, & Vlassara, 1992; Schmidt et al., 1995), resulting in cellular and vascular dysfunction.

Intracellular hyperglycemia is the primary event in AGE formation (Brownlee, 2001; Degenhardt, Thorpe, & Baynes, 1998). AGEs are associated with the development, severity, and progression of diabetic microvascular complications in humans (Anitha, Sampathkumar, Balasubramanyam, & Rema, 2007; Sourris, Harcourt, & Forbes, 2009). In fact, skin expression of AGE was a better predictor of microvascular complications than HbA1c (Monnier et al., 1999). AGE inhibition had beneficial effects on diabetic microvascular complications in rodent studies (Hellweg & Hartung, 1990; Yagihashi, Kamijo, Baba, Yagihashi, & Nagai, 1992).

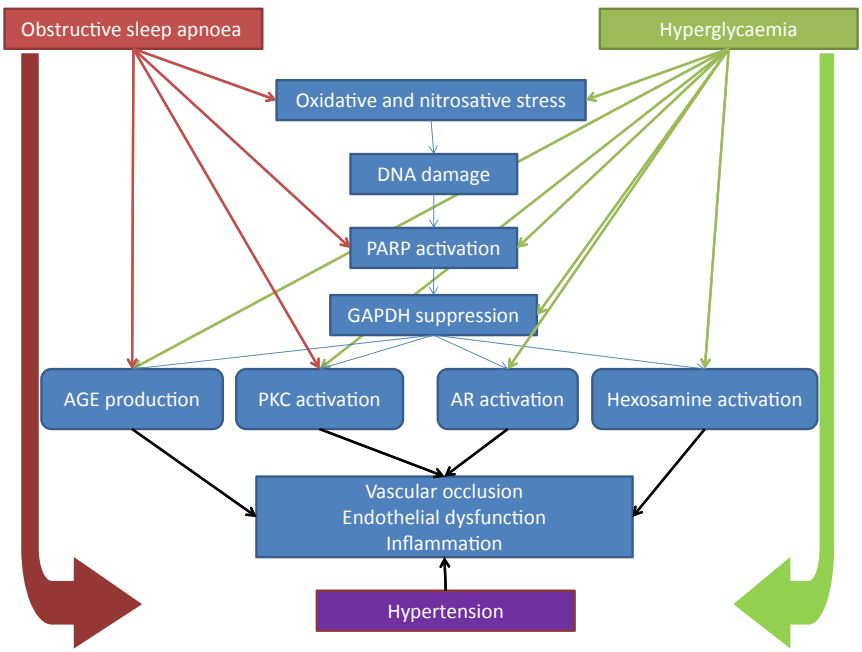

FIGURE 1 Summary of the mechanisms linking hyperglycemia to microvascular dysfunction and the possible mechanisms by which OSA might contribute to the development and/or progression of microvascular complications in patients with T2D. AGE: Advanced glycation end product; PKC: protein kinase C; AR: aldose reductase; PARP: poly ADP ribose polymerase. Both OSA and hyperglycaemia share similar molecular mechanisms, including oxidative stress, PKC activation, and AGE production. Our own work has shown that patients with OSA and T2D have increased oxidative and nitrosative stress and impaired microvascular complications compared to patients with T2D only, and that patients with OSA and T2D have PARP activation compared to patients without T2D.

Protein Kinase C

Intracellular hyperglycemia results in an increased synthesis of diacylglycerol (DAG), which activates protein kinase C (PKC; Brownlee, 2005). PKC activation leads to decreased production of endothelial nitric oxide synthase (eNOS); increased endothelin-1, tissue growth factor-β (TGF-β), vascular endothelial growth factor (VEGF), and plasminogen activator inhibitor-1 (PAI-1); and activation of nuclear factor-KB (NF-KB) (Brownlee, 2005). The net effect is inflammation, endothelial and vascular dysfunction, and cellular/tissue damage (Brownlee, 2005). PKC inhibition in animal studies prevented the development of DR, DN, and DPN (Brownlee, 2005; Cotter, Jack, & Cameron, 2002; Ishii et al., 1996; Koya et al., 2000). In humans, ruboxistaurin (a PKC inhibitor) has been shown to have a beneficial effect on vision, the progression of macular edema, and albuminuria levels in patients with T2D (Aiello et al., 2006; Tuttle et al., 2005).

The Polyol Pathway

The polyol pathway was the first pathway to be defined linking hyperglycemia to microvascular complications (Brownlee, 2001; Gabbay, Merola, & Field, 1966). Aldose reducatse (AR), the first enzyme in this pathway, has low affinity to glucose at normal concentrations; however, in diabetes, increasing amounts of glucose are converted by AR to sorbitol. Sorbitol is metabolized to fructose by sorbitol dehydrogenase (SDH), which reduces NAD^+ to NADPH during this process (Brownlee, 2001). The oxidation of sorbitol by NAD^+ increases the cytosolic NADH:NAD^+ ratio, which inhibits glyceraldehyde 3-phosphate dehydrogenase (GAPDH) and leads to increased triose phosphate levels, which results in increased AGE and DAG (Brownlee, 2001; Williamson et al., 1993). Furthermore, activation of the polyol pathway increases oxidative stress by reducing the antioxidant defense system (Brownlee, 2001; Burg & Kador, 1988). AR inhibition has been shown to improve DPN (Askwith, Zeng, Eggo, & Stevens, 2009; Obrosova, 2009).

The Hexosamine Pathway

In the hexosamine pathway, some of the fructose-6-phosphate resulting from glucose metabolism is converted to glucosamine-6 phosphate by glutamine:fructose-6 phosphate amidotransferase and finally to uridine diphosphate *N*-acetyl glucosamine (Brownlee, 2005). *N*-acetyl glucosamine results in changes gene expression that favors microvascular occlusion/dysfunction such increased PAI-1 expression (Brownlee, 2005).

Oxidative Stress and GAPDH Inhibition

A common feature of cells that are damaged by hyperglycemia is the presence of free radical species, such as reactive oxygen species (ROS) and reactive nitrogen species (Du et al., 2000; Nishikawa et al., 2000). Normalizing mitochondrial ROS levels prevents the activation of PKC, the polyol and hexosamine pathways, and AGE production (Nishikawa et al., 2000), suggesting an important role for hyperglycemia-induced oxidative stress in the pathogenesis of microvascular disease.

ROS activates these pathways via the key glycolytic enzyme GAPDH (Brownlee, 2005). GAPDH activity is reduced in patients and animals with diabetes, and inhibition of GAPDH does not occur when ROS production is prevented (Brownlee, 2005; Du et al., 2000). When GAPDH activity is inhibited, the levels of all the upstream glycolytic intermediates increase, including methylglyoxal (increasing AGE formation), DAG (activates PKC), fructose-6 phosphate (activating the hexosamine pathway), and intracellular glucose levels (activating the polyol pathway) (Brownlee, 2005). In addition to the excess in superoxide production, hyperglycemia results in reduction in the antioxidant defense system, further exacerbating oxidative stress in diabetes (Packer & Tritschler, 1996).

Polymers of ADP-Ribose Polymerase

Oxidative stress inhibits GAPDH via activation of polymers of ADP-ribose polymerase (PARP). Poly(ADP-ribosyl)ation is the process by which polymers of ADP-ribose (PAR) are attached via an ester bond to glutamic acid, aspartic acid, or lysine residues, mediated by PARP1 and PARP2 (Woodhouse & Dianov, 2008). PARP1 binds as a homodimer to single-strand DNA breaks, where it is activated and catalyzes the cleavage of NAD^+, forming nicotinamide and ADP-ribose, the polymers of which are added to nuclear proteins (Pacher & Szabo, 2008). Increased oxidative stress results in DNA damage and PARP1 activation (Vincent, Russell, Low, & Feldman, 2004). Although this is beneficial, PARP hyperactivation in diabetes leads to detrimental effects by increasing NADH:NAD^+ ratio and worsening the effects of the flux via the polyol pathway and inhibiting GAPDH, which requires NAD^+ as a cofactor (Brownlee, 2005; Du et al., 2003; Pacher & Szabo, 2008). PARP inhibition has been shown to improve DPN (Obrosova et al., 2004; Obrosova et al., 2008).

WHY MIGHT OSA CONTRIBUTE TO THE DEVELOPMENT AND PROGRESSION OF DIABETIC MICROVASCULAR COMPLICATIONS?

OSA is associated with IR, hyperglycemia, and hypertension, all of which are major risk factors for vascular disease in patients with diabetes. In addition, many of the molecular consequences of OSA are similar to those caused by hyperglycemia (see below). Hence, it is plausible that OSA could

result in the development and/or progression of diabetic microvascular complications (Figure 1).

OSA, IR, and Hyperglycemia

In patients without diabetes, many cross-sectional studies showed an association between OSA and IR (Tahrani, Ali, et al., 2013); this association seems to be stronger in patients with excessive daytime sleepiness, independent of the severity of OSA (Barcelo et al., 2008; Nena et al., 2012). One longitudinal study found that OSA and nocturnal hypoxemia were independent predictors of worsening IR over an 11-year follow-up after adjustment for age, baseline body mass index (BMI), hypertension, BMI change over follow-up and continuous positive airway pressure (CPAP) treatment (Lindberg et al., 2012). In patients with T2D, OSA was also found to be associated with IR (Hermans, Ahn, Mahadeb, & Rousseau, 2013). Similar findings were also found in lean individuals, suggesting that the relationship between IR and OSA is independent of obesity (Lin et al., 2012; Pamidi et al., 2012). CPAP treatment has been shown to improve IR (Iftikhar, Khan, Das, & Magalang, 2013; Yang, Liu, & Yang, 2012; Yang, Liu, Yang, & Luo).

Several studies have shown that OSA and OSA severity are associated with poorer glycemic control (HbA1c and/or fasting plasma glucose) despite adjustment for confounders in some studies (Aronsohn, Whitmore, Van Cauter, & Tasali, 2010; Drager et al., 2009; Kosseifi et al., 2010; Papanas et al., 2009; Pillai, Warren, Gunathilake, & Idris, 2011). The adjusted mean increase in HbA1c between patients with and without OSA was 0.7–3.7%, depending on the study population and OSA severity (Tahrani, Ali, et al., 2013). The association between HbA1c and apnea–hypopnea index (AHI) seems stronger during rapid eye movement (REM) compared to non-REM sleep (Grimaldi, Beccuti, Touma, Van Cauter, & Mokhlesi, 2014). A study found that nocturnal hypoxemia rather than the AHI was associated with HbA1c in T2D (Tamura, Kawano, Watanabe, & Kadota, 2012). The impact of CPAP on glycemic measures in T2D is unclear as some noncontrolled trials showed a beneficial effect, while the only randomized controlled trial to date did not show such benefit (Babu, Herdegen, Fogelfeld, Shott, & Mazzone, 2005; Brooks et al., 1994; Dawson et al., 2008; Harsch et al., 2004; Hassaballa, Tulaimat, Herdegen, & Mokhlesi, 2005; Pallayova, Donic, & Tomori, 2008; Shpirer, Rapoport, Stav, & Elizur, 2012; West, Nicoll, Wallace, Matthews, & Stradling, 2007). However, this could be related to the duration of CPAP usage, as shown in an abstract (Tasali et al., 2013).

OSA and Hypertension

The link between OSA and sustained hypertension and/or the lack of nocturnal dipping in BP and the beneficial impact of CPAP treatment on BP in patients without diabetes are well established in prospective and interventional studies (Barbe et al., 2010; Guillot et al., 2013; Hla et al., 2008; Joaquin et al., 2010; Nieto et al., 2000; Peppard, Young, Palta, & Skatrud, 2000). Data in patients with diabetes are limited, but a retrospective cohort study in patients with OSA and T2D showed that CPAP was associated with a mean change of −6.81 mmHg (95% CI: −9.94 to −3.67 mmHg) and −3.69 mmHg (−5.53 to −1.85 mmHg) in systolic and diastolic BP, respectively, after 9–12 months of treatment (Prasad, Carley, Krishnan, Weaver, & Weaver, 2012). A randomized parallel group intervention trial showed similar results after 3 months of CPAP treatment (Myhill et al., 2012).

OSA and AGE

AGE formation and RAGE expression were identified as regulators of hypoxia-induced tissue stress in animal and in-vivo studies (Chang et al., 2008; Pichiule, Chavez, Schmidt, & Vannucci, 2007). Intermittent hypoxia, as occurs in OSA, is associated with ischemia-reperfusion injury, resulting in increased RAGE expression (Yan, Ramasamy, & Schmidt, 2009). Patients with OSA have higher serum AGE levels compared to controls, and OSA severity has been correlated with serum AGE levels (Tan et al., 2006).

OSA and PKC

Intermittent hypoxia has been shown to increase DAG levels and stimulate certain isoforms of the PKC family (Allahdadi, Duling, Walker, & Kanagy, 2008; Goldberg, Zhang, & Steinberg, 1997). OSA has been associated with many of the consequences of PKC activation in human studies, including reduction in eNOS and phosphorylated eNOS expression, which was reversible with CPAP (Jelic et al., 2008); increased plasma endothelin-1 levels (Gjorup, Wessels, & Pedersen, 2008); increased VEGF levels, which were lowered by CPAP (Lavie et al., 2002; Schulz, Hummel, Heinemann, Seeger, & Grimminger, 2002; Valipour et al., 2004); increased PAI-1, which was lowered by CPAP (von Kanel, Loredo, Ancoli-Israel, & Dimsdale, 2006; von Kanel, Loredo, Ancoli-Israel, Mills, & Dimsdale, 2007); and increased NF-KB (Htoo et al., 2006; Williams & Scharf, 2007).

OSA and Oxidative and Nitrosative Stress

Many markers have been used to demonstrate the relationship between OSA and oxidative stress, including plasma, exhaled breath condensate, and urinary 8-isoprostane levels; plasma levels of malondialdehyde (MDA); urinary o,o′-dityrosine; plasma levels of thiobarbituric acid reactive substances; urine levels of 8-hydroxy-2′-deoxyguanosine

(8-OhdG); and ROS production in monocytes, granulocytes, and neutrophils upon in vitro stimulation (Arnardottir, Mackiewicz, Gislason, Teff, & Pack, 2009). Intermittent hypoxia was associated with mitochondrial dysfunction and increased ROS production (Lavie, 2009; Peng, Yuan, Overholt, Kumar, & Prabhakar, 2003). Patients with OSA have higher ROS levels than those without OSA (Lavie, 2009; Schulz, Mahmoudi, et al., 2000) and have higher ROS production in neutrophils and monocytes (Dyugovskaya, Lavie, & Lavie, 2002; Schulz, Mahmoudi, et al., 2000). In addition, several studies showed that patients with OSA have increased levels of lipid peroxidation (interaction between free radicals and lipids) (Barcelo et al., 2000), oxidized low-density lipoprotein (LDL; Kizawa et al., 2009), protein carbonylation (interaction between free radicals and protein) (Vatansever, Surmen-Gur, Ursavas, & Karadag, 2011), and 8-OhdG (marker of DNA oxidation) (Lavie, 2012). The increased oxidative stress observed in OSA is reversible with OSA treatment (CPAP and mandibular advancement devices) (Christou et al., 2009; Itzhaki et al., 2007). Similar to hyperglycemia, OSA is also associated with reduced antioxidant capacity, which can be reversed by CPAP treatment (Barcelo et al., 2006). OSA was also associated with increased nitrosative stress (Jelic et al., 2010), which is reversible by CPAP (Jelic et al., 2008).

Studies have extended these findings to patients with T2D. Patients with OSA and T2D were found to have higher serum nitrotyrosine and plasma lipid peroxide levels compared to patients with T2D only, suggesting increased nitrosative and oxidative stress in patients with OSA and T2D over and above that caused by T2D only (Tahrani, Ali, et al., 2012). OSA severity correlated with severity of nitrosative and oxidative stress in patients with T2D (Tahrani, Ali, et al., 2012).

OSA and Inflammation

OSA might be related to inflammation via different mechanisms, including increased oxidative stress, PKC activation, and increased release of free fatty acids from the adipose tissue. Sleep fragmentation/restriction is also associated with increased interleukin (IL)-6 and tumor necrosis factor (TNF)-α (Vgontzas et al., 1999). In vivo and in vitro studies have shown that intermittent hypoxia can lead to increased hypoxia-inducible factor-1 (HIF-1) (Peng et al., 2003; Peng et al., 2006), which can result in increased inflammation (Cramer et al., 2003). In addition to intermittent hypoxia, other OSA-related factors can result in increased HIF-1, including oxidative stress and NF-κB activation (Prabhakar, Kumar, & Nanduri, 2010; Rius et al., 2008).

Several cytokines, such as IL-6, IL-8, TNF-α, C-reactive protein (CRP), granulocyte chemotactic protein-2 (GCP-2), and monocyte chemotactic protein-1 (MCP-1) have been shown to be associated with OSA independent of obesity (Alberti et al., 2003; Arnardottir et al., 2009; Bravo et al., 2007; Ciftci, Kokturk, Bukan, & Bilgihan, 2004; Hayashi et al., 2006; Liu et al., 2000; Minoguchi et al., 2005; Ohga et al., 2003; Ursavas et al., 2007; Vgontzas et al., 2000). CPAP treatment was effective in reducing these cytokines (Minoguchi et al., 2004; Yokoe et al., 2003). Not all studies showed a relationship between OSA and inflammation (Imagawa et al., 2004; Sharma et al., 2008), with obesity being the main confounder.

In OSA, polymorphonuclear cells, monocytes, and T lymphocytes have been shown to have increased adhesion molecules (selectins and integrins), increased avidity to endothelial cells, and increased prolonged lifespan of active polymorphonuclear cells compared to controls (Dyugovskaya, Lavie, Hirsh, & Lavie, 2005; Dyugovskaya et al., 2002; Dyugovskaya, Lavie, & Lavie, 2005; Dyugovskaya, Polyakov, Cohen-Kaplan, Lavie, & Lavie, 2012; Dyugovskaya, Polyakov, Lavie, & Lavie, 2008; Lavie, 2012; Lavie, Dyugovskaya, & Polyakov, 2008; Schulz, Mahmoudi, et al., 2000), which can lead to endothelial dysfunction in combination with oxidative stress (Tahrani & Ali, 2014). Endothelial cells from patients with OSA showed increased expression of intercellular adhesion molecule 1 (ICAM-1), vascular cell adhesion molecule (VCAM), E-selectin, and P-selectin compared to controls, which might be reversible with CPAP (Chin et al., 2000; Minoguchi et al., 2007; Ohga et al., 2003; Ursavas et al., 2007; Zamarron-Sanz, Ricoy-Galbaldon, Gude-Sampedro, & Riveiro–Riveiro, 2006).

OSA and Endothelial Dysfunction

Multiple deficits might contribute to the development of endothelial dysfunction in patients with OSA, including IR, hypertension, autonomic dysfunction, PKC activation, increased AGE formation, oxidative and nitrosative stress, and inflammation (Dimitropoulos et al., 2014; Kahal, Tahrani, George, Barlow, & Malik, 2013; Tahrani & Ali, 2014; Tahrani, Ali, et al., 2012; Tahrani, Ali, et al., 2013).

Patients with OSA have been shown to have impaired vasodilatation. Circulating and endothelial levels of nitric oxide (NO) are reduced in patients with OSA and can improve after CPAP (Ip et al., 2000; Jelic et al., 2008; Schulz, Schmidt, et al., 2000). Several studies have shown that endothelial-dependent vasodilatation in OSA patients was impaired independent of hypertension (Carlson, Rangemark, & Hedner, 1996), obesity (Kato et al., 2000), and cardiovascular risk factors (Nieto, Herrington, Redline, Benjamin, & Robbins, 2004). A study that used laser Doppler flowmetry to examine forearm skin microcirculation found that OSA was associated with lower baseline blood flow compared to subjects without OSA and that the response to acetylcholine and sodium nitroprusside was not impaired by OSA (Yim-Yeh et al., 2011). In one study, it was suggested that OSA was associated with impaired

nitric oxide production as CPAP treatment improved flow-mediated vasodilatation of the brachial artery and lowered asymmetric NG,NG-dimethylarginine (ADMA), which is an endogenous inhibitor of eNOS (Ohike et al., 2005). Compared to BMI- and age-matched controls, patients with OSA had a higher pulse wave velocity, indicating the presence of atherosclerosis (Nagahama et al., 2004).

In addition to the impaired vasodilatation, OSA might be associated with increased production of vasoconstrictors, as some studies have shown increased endothelin-1 in patients with OSA (Gjorup et al., 2008). Some studies have also shown that OSA was associated with impaired endothelial repair (judged by circulating endothelial progenitor cells) (Jelic et al., 2008) and increased endothelial apoptosis (El Solh, Akinnusi, Baddoura, & Mankowski, 2007). CPAP treatment was shown to improve flow-mediated vasodilatation (Ip, Tse, Lam, Tsang, & Lam, 2004), endothelial-dependent vasodilatation (Lattimore, Wilcox, Skilton, Langenfeld, & Celermajer, 2006), endothelial repair capacity (El Solh et al., 2007), and vasoreactivity (Imadojemu et al., 2002).

In patients with T2D, OSA, AHI, and oxygen desaturation index (ODI) were all associated with impaired baseline flow and impaired response to sodium nitroprusside after adjustment for confounders; in addition, nadir nocturnal oxygen saturation was associated with impaired response to sodium nitroprusside (Tahrani, Ali, et al., 2012). These findings can be either due to impaired NO production or impaired action due to increased oxidative stress in patients with OSA.

OSA AND DIABETIC MICROVASCULAR COMPLICATIONS

We have described the possible links between OSA and diabetic microvascular complications. Epidemiologically, several studies have confirmed the association between OSA and diabetic microvascular complications; these studies, however, are mostly cross-sectional, showing association rather than causation. There is also a lack of clarity on whether OSA contributes to the development or the progression of these complications (or both). A major confounding factor for the association between OSA and microvascular complications is obesity; statistical adjustments and matching were used in some studies to take into account this confounding effect. Longitudinal studies and interventional trials assessing the impact of OSA on diabetes-related microvascular outcomes are currently ongoing.

OSA and DR

OSA has been associated with DR in cross-sectional studies (Rudrappa, Warren, & Idris, 2012; Shiba, Maeno, Saishin, Hori, & Takahashi, 2010; Tahrani, Dodson, et al., 2013). Although the study populations were very different, all the studies showed an association between OSA, hypoxemia, and DR. In Japanese patients undergoing vitreous surgery, ODI was higher in patients with proliferative DR compared to those without proliferative DR, and higher oxygen saturations were protective against proliferative DR after adjustment for age, HbA1c, and hypertension (Shiba et al., 2010). In a UK-based study that had a mixed population from primary and secondary care and included only men with T2D, OSA was independently associated with DR and maculopathy after adjustment for major DR risk factors, including BMI (Tahrani, Dodson, et al., 2013). Another study included men and women of South Asian and white European origins recruited from secondary care in the UK; patients with OSA were 3–4 times more likely to have sight-threatening DR, preproliferative/proliferative DR, or maculopathy after adjustment for a wide range of confounders and DR risk factors (Tahrani, Dodson, et al., 2013). OSA was also associated with angle neovascularization in Japanese patients with proliferative DR (Shiba et al., 2011).

Only one study to date assessed the longitudinal impact of OSA on DR; this study has shown that OSA was an independent predictor of the development of advanced DR in patients with T2D over a 5-year follow-up period (adjusted odds ratio (OR): 6.6, 95% CI: 1.2–35.1, $p=0.03$; Tahrani, Dodson, et al., 2013). Interestingly, this study has also shown that patients who were compliant with CPAP were at lower risk of developing advanced DR over the follow-up period compared to those who were not compliant, despite no significant differences between the groups in regards to demographic, biochemical, and clinical profiles. These results, however, are only observational and not interventional; hence, they cannot account for other confounders, such as the causes of compliance or noncompliance. In an uncontrolled, hypothesis-generating interventional study, 6 months of CPAP treatment was associated with improvement in visual acuity without affecting macular edema/thickness, suggesting a possible improvement in function due to the correction of hypoxemia rather than actual structural improvement (Mason et al., 2012).

OSA and DN

Studies regarding the relationship between OSA and DN are limited. The most comprehensive study to date is a cross-sectional and longitudinal UK-based study of patients with T2D; it showed that OSA was associated with DN after adjustment for possible confounders (adjusted OR: 2.64; 95% CI: 1.13–6.16, $p=0.02$; Tahrani, Ali, et al., 2013). Higher nadir nocturnal oxygen saturation was associated with less DN (adjusted OR: 0.96, 95% CI: 0.93–1.00, $p=0.05$; Tahrani, Ali, et al., 2013). The estimated glomerular filtration rate (eGFR) decline over a 2.5-year follow-up of the same study was

greater in patients with compared to those without OSA (median (interquartile range): −6.8% (−16.1 to 2.2%) vs −1.6% (−7.7 to 5.3%), $p = 0.002$) and that baseline OSA and AHI were independent predictors of study-end eGFR (Tahrani, Ali, et al., 2013). In a cross-sectional study of Japanese patients with T2D, ODI ≥5 was independently associated with microalbuminuria and DN in women but not in men (Furukawa et al., 2013). Similar studies were found in another cross-sectional study in which snoring (as surrogate marker of OSA) was found to be independently associated with microalbuminuria in patients with diabetes (Ozol et al., 2011). However, another cross-sectional study found that OSA was not associated with microalbuminuria in patients with T2D (Buyukaydin et al., 2012). These findings could be due to the small sample size of this study ($n = 52$) or to methodological issues because polysomnography was performed in high-risk patients only.

OSA and Diabetic Neuropathy

Only one cross-sectional study assessed the association between OSA and diabetic neuropathy. OSA was found to be independently associated with DPN (adjusted OR: 2.82, 95% CI: 1.44–5.52) and foot insensitivity (adjusted OR: 3.97; 95% CI: 1.80–8.74) after adjustment for confounders (Tahrani, Ali, et al., 2012). AHI and nocturnal hypoxemia were also associated with DPN (Tahrani, Ali, et al., 2012). Unpublished data from the same study showed that OSA was associated with lower intraepidermal nerve fiber density in skin biopsies obtained from the midthigh (Tahrani, unpublished data).

OSA is also associated with DAN and increased sympathetic activity (Grassi et al., 2005). It is likely that both the recurrent hypoxia (Xie, Skatrud, Puleo, & Morgan, 2001) and recurrent arousals (Loredo, Ziegler, Ancoli-Israel, Clausen, & Dimsdale, 1999) contribute to the activation of the sympathetic system in patients with OSA. However, the relationship between OSA and DAN is likely to be bidirectional because obese patients with DAN develop more frequent and more prolonged hypopnea/apnea in comparison to those without DAN, whether or not they had T2D (Bottini, Redolfi, Dottorini, & Tantucci, 2007).

SUMMARY AND CONCLUSIONS

OSA is very common in patients with T2D and is associated with increased IR, hyperglycemia, hypertension, and obesity. In addition, OSA has similar molecular signatures to those of hyperglycemia, causing hypertension and increased oxidative and nitrosative stress, PARP activation, activation of PKC and the polyol pathway, and increased inflammation and endothelial dysfunction. Hence, it is plausible that OSA contributes to the development of diabetic microvascular complications, which have a significant impact on the morbidity and mortality of patients with diabetes and a significant economic burden to health care systems. Epidemiological studies have shown that OSA is associated with DR, DN, DPN, and CAN in cross-sectional studies independent of possible confounders. Prospective studies showed that OSA predicts eGFR decline and the development of advanced DR in patients with T2D. Early observational data suggest a beneficial impact of OSA treatment on DR and DN. However, interventional studies are currently ongoing.

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Chapter 24

Obstructive Sleep Apnea Increases Hemoglobin A1c Levels: Mechanisms and Consequences

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Chapter Outline

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INTRODUCTION

Obstructive sleep apnea (OSA) is a chronic condition characterized by repetitive episodes of upper airway obstruction, apneas, and arousals during sleep. Over the past two decades, numerous studies have shown an independent association between OSA and impaired glucose metabolism (Elmasry et al., 2001; Grunstein, Stenlof, Hedner, & Sjöström, 1995; Harsch et al., 2004; Ip, Lam, Ho, & Lam, 2000; Ip et al., 2002; Meslier et al., 2003; Punjabi et al., 2004; Punjabi et al., 2002; Seicean et al., 2008; Stoohs, Facchini, & Guilleminault, 1996; Strohl, 1996; Strohl et al., 1994; Tamura, Kawano, Watanabe, & Kadota, 2008; Vgontzas et al., 2000). Moreover, several prospective studies have shown that OSA is independently associated with an increasing risk for new onset of diabetes mellitus (DM) (Botros et al., 2009; Lindberg, Berne, Elmasry, Hedner, & Janson, 2006; Marshall et al., 2009; Muraki et al., 2010), although a conflicting result exists (Reichmuth, Austin, Skatrud, & Young, 2005). Hemoglobin A1c (HbA1c) is a marker of an individual's average blood glucose level for the preceding 2–3 months (Nathan et al., 2008) and is therefore widely used as a major index for monitoring glycemic control in diabetic patients (American Diabetes Association, 2011). Furthermore, it has been shown that HbA1c levels are independently associated with mortality and/or subsequent cardiovascular diseases in nondiabetic and diabetic subjects (Gerstein et al., 2005; Ikeda et al., 2013; Kerr, Partridge, Knott, & Thomas, 2011; Khaw et al., 2001; Lauritzen, Sandbaek, Carlsen, & Borch-Johnsen, 2012; van't Riet et al., 2012; Selvin et al., 2005; Selvin et al., 2010). Therefore, it is clinically meaningful to clarify whether OSA affects HbA1c levels. In this chapter, the author will focus on the association between OSA severity and HbA1c levels and review the current evidence on this association.

ASSOCIATION BETWEEN OSA SEVERITY AND HBA1C LEVELS IN OSA PATIENTS

A few cross-sectional studies (Elmasry et al., 2001; Priou et al., 2012; Tamura, Kawano, Watanabe, & Kadota, 2012) have examined the association between OSA severity and HbA1c levels in patients undergoing a sleep study for suspected OSA (Table 1). Elmasry et al. (2001) found that the 4% oxygen desaturation index (ODI) and lowest arterial oxyhemoglobin saturation (SpO_2) were independently associated with HbA1c levels in 116 hypertensive men. A subgroup analysis showed that the apnea–hypopnea index (AHI), 4% ODI, and lowest SpO_2 were independently associated with HbA1c levels even in 83 men with a normal level of fasting glucose. These findings suggest a positive association between OSA severity and elevated HbA1c levels in patients with OSA. However, that study did not perform full polysomnography, a gold standard for diagnosing OSA. Priou et al. (2012) examined the association between OSA

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TABLE 1 Previous Studies Concerning the Association between OSA Severity and HbA1c Levels in Patients With Suspected OSA

Author (year)	Sample size	Comorbid conditions	Type of sleep studies	Results
Elmasry et al. (2001)	116	Suspected OSA + hypertension	Respiratory recording	4% ODI and lowest SpO_2 were independently associated with HbA1c.
Priou et al. (2012)	2139	Suspected OSA	Respiratory recording or full polysomnography	Increasing OSA severity was independently associated with HbA1c >6.0%.
Tamura et al. (2012)	330	Suspected OSA	Full polysomnography	Lowest SpO_2 was independently associated with HbA1c.

OSA: obstructive sleep apnea, HbA1c: hemoglobin A1c, ODI: oxygen desaturation index, SpO_2: arterial oxyhemoglobin saturation.

severity and HbA1c levels in 2139 patients without known DM undergoing either polysomnography or respiratory recordings for suspected OSA. Patients with self-reported diabetes, use of medications for DM, or HbA1c≥6.5% were excluded. A dose–response relationship was observed between the AHI and percentage of HbA1c >6.0%, ranging from 10.8% for AHI <5 to 34.2% for AHI ≥50. After adjustment for confounding variables, odds ratios for HbA1c levels were 1 (reference), 1.4 (95% confidence interval [CI], 0.84–2.32), 1.80 (95% CI, 1.19–2.72), 2.02 (95% CI, 1.31–3.14), and 2.96 (95% CI, 1.58–5.54) for AHI values <5, 5 to <15, 15 to <30, 30 to <50, and ≥50, respectively. Furthermore, increasing hypoxemia during sleep (mean SpO_2, 3% ODI, and time with SpO_2 <90%) was also independently associated with the odds of HbA1c >6.0%. They concluded that increasing OSA severity is independently associated with HbA1c >6.0% in adults without known DM. However, that study performed full polysomnography in only 563 of the 2139 patients (26.3%). We (Tamura et al., 2012) investigated the association between OSA severity assessed by full polysomnography and HbA1c levels in 330 subjects who were clinically suspected to have OSA. All patients who had not been diagnosed as having DM underwent a 75 g oral glucose tolerance test. Patients using hypoglycemic agents were excluded. The 330 subjects were divided into the following three subgroups: 164 with normal glucose tolerance (NGT), 111 with impaired glucose tolerance (IGT), and 55 with DM. HbA1c levels differed significantly among subjects with AHI <5, those with 5≤AHI<15, those with 15≤AHI<30, and those with AHI ≥30 in all subjects, NGT subgroup, and DM subgroup. HbA1c levels were correlated positively with the AHI in all subjects, NGT subgroup, and IGT subgroup and negatively with the lowest SpO_2 in all subjects and all subgroups. Multiple regression analyses showed that ln (lowest SpO_2) was independently associated with ln (HbA1c) in all subjects and all subgroups and that ln (AHI) was independently associated with ln (HbA1c) only in the IGT subgroup. These findings indicate that HbA1c levels increase in association with the magnitude of the lowest SpO_2 irrespective of the glucose tolerance status, thus suggesting that OSA-induced hypoxemia increases an individual's average blood glucose level irrespective of the glucose tolerance status.

In summary, the current evidence suggests an independent association between OSA severity and HbA1c levels in patients with OSA. Of great interest is that this association is observed even in nondiabetic patients with OSA. Given an independent association between HbA1c levels and subsequent cardiovascular diseases in nondiabetic and diabetic adults (Gerstein et al., 2005; Ikeda et al., 2013; Kerr et al., 2011; Khaw et al., 2001; Lauritzen et al., 2012; van't Riet et al., 2012; Selvin et al., 2005; Selvin et al., 2010) and an independent association between severe OSA and cardiovascular events (Marin, Carrizo, Vicente, & Agusti, 2005), an independent association between OSA severity and HbA1c levels may be involved in the pathogenesis of the cardiovascular complications of OSA.

ASSOCIATION BETWEEN OSA SEVERITY AND HbA1c LEVELS IN DIABETIC PATIENTS

Can OSA affect glycemic control in diabetic patients? Since OSA is highly prevalent in diabetic patients (Foster et al., 2009; Laaban et al., 2009; Resnick et al., 2003), this question is very important in the management of diabetic patients with OSA. Several cross-sectional studies (Aronsohn, Whitmore, Van Cauter, & Tasali, 2010; Grimaldi, Beccuti, Touma, Van Cauter, & Mokhlesi, 2014; Lam et al., 2010; Pillai, Warren, Gunathilake, & Idris, 2011) have examined the association between OSA severity and HbA1c levels in diabetic patients (Table 2). Aronsohn et al. (2010) examined OSA severity assessed by full polysomnography and HbA1c levels in 60 diabetic patients and found an independent association between the AHI and HbA1c levels. Compared with patients without OSA (AHI <5), the adjusted (age, sex, race, body mass index, number of diabetes medications, level of exercise, years of diabetes, and total sleep time) HbA1c level was increased by 1.49% in those with mild OSA (5≤AHI<15), 1.93% in those with moderate OSA (15≤AHI<30), and 3.60% in those with severe OSA (AHI ≥30). They concluded that increased OSA severity is

TABLE 2 Previous Studies Concerning the Association between OSA Severity and HbA1c Levels in Diabetic Patients

Author (year)	Sample size	Type of sleep studies	Results
Aronsohn et al. (2010)	60	Full polysomnography	AHI was independently associated with HbA1c levels.
Lam et al. (2010)	165	Full polysomnography	AHI was not independently associated with HbA1c levels.
Pillai et al. (2011)	52	Respiratory recording	AHI was independently associated with HbA1c levels.
Grimaldi et al. (2013)	115	Full polysomnography	AHI during REM sleep, but not during non-REM sleep, was independently associated with HbA1c levels.

OSA: obstructive sleep apnea, HbA1c: hemoglobin A1c, AHI: apnea–hypopnea index, REM: rapid eye movement.

independently associated with poor glycemic control in diabetic patients. Pillai et al. (2011) examined the association between OSA severity assessed by respiratory recording and HbA1c levels in 52 diabetic patients and found that the AHI was independently associated with increased HbA1c levels. The adjusted (age, gender, body mass index, duration of diabetes, and insulin dose) HbA1c level were 8.62% for no OSA (AHI <5), 9.36% for mild OSA (5≤AHI<15), 10.61% for moderate OSA (15≤AHI<30), and 9.91% for severe OSA (AHI ≥30), which suggested a plateau effect between OSA severity and HbA1c levels. In contrast, Lam et al. (2010) found no significant association between any sleep parameters assessed by full polysomnography and HbA1c levels in 165 diabetic patients (detailed data are not shown in the paper). In that study, 57% of the patients received insulin therapy, which means that more than half of the patients had advanced DM. OSA might have only a minor influence on glycemic control in patients with advanced DM, who probably have a large amount of loss of pancreatic beta-cells.

There is a paper suggesting a significant difference in the impact on glycemic control between OSA during rapid eye movement (REM) sleep and OSA during non-REM sleep. Grimaldi et al. (2013) examined the associations of the AHI during REM sleep and the AHI during non-REM sleep with HbA1c levels in 115 diabetic patients and found that the AHI during REM sleep, but not during non-REM sleep, was independently associated with increased HbA1c levels. Based on the distribution of cumulative REM sleep in their cohort, which indicated a dominance of REM sleep during the latter part of the sleep period, they assumed the following: continuous positive airway pressure (CPAP) use after the first 4 h after lights off would leave 60% of REM sleep untreated, with a decrease in HbA1c by 0.25%; and 7 h of CPAP use per night would cover >85% of REM sleep, with a decrease in HbA1c by 1%. Their observations and assumptions are very interesting but require validation.

In summary, the current evidence suggests a positive association between OSA severity and poor glycemic control in diabetic patients. However, it is unclear as to whether this association is observed in patients with advanced DM. Further studies are needed to clarify the interactions among OSA severity, glycemic control, and DM severity.

EFFECT OF CPAP ON HbA1C LEVELS

A suggestive association between OSA severity and glycemic control in diabetic patients would lead to the following hypothesis that CPAP, a first-line therapy for OSA, may be a potential strategy to improve glycemic control in diabetic patients with OSA. There are six observational (Babu, Herdegen, Fogelfeld, Shott, & Mazzone, 2005; Dawson et al., 2008; Harsch et al., 2004; Shpirer, Rapoport, Stav, & Elizur, 2012; Smurra et al., 2011; Steiropoulos et al., 2009) and two randomized controlled (Sharma et al., 2011; West, Nicoll, Wallace, Matthews, & Stradling, 2007) studies to test the hypothesis (Table 3).

In an observational study involving 25 diabetic patients with OSA, Babu et al. (2005) found a significant reduction in HbA1c levels after approximately 3 months of CPAP therapy in 17 diabetic patients with a baseline HbA1c level of >7% ((mean ± SD) 9.2% ± 2.0% to 8.6% ± 1.8%, $p = 0.02$). Furthermore, the reduction in HbA1c levels was significantly correlated with the number of days of CPAP use in patients who used CPAP for more than 4 h/day ($r = 0.74$, $p = 0.006$). These results suggest that CPAP may improve glycemic control in proportion to the duration of CPAP treatment in diabetic patients with OSA who are compliant CPAP users. Steiropoulos et al. (2009) examined the effect of 6-month treatment with CPAP on HbA1c levels in 56 nondiabetic patients with OSA and found a significant reduction in HbA1c levels without significant changes in body weight and insulin sensitivity, as assessed by the homeostatic model assessment, only in patients with mean CPAP use of ≥4 h/day ((mean ± SD) 5.55% ± 0.4% to 5.38% ± 0.45%, $p = 0.004$). Shpirer et al. (2012) found a significant reduction in HbA1c levels after 3–6 months treatment with CPAP in 30 OSA patients without known DM ((mean ± SD) 6.47% ± 0.67%

TABLE 3 Previous Prospective Observational and Randomized Controlled Studies to Investigate the Effect of CPAP on HbA1c Levels in Patients With OSA

Author (year)	Study type	Sample size	Comorbid conditions	Duration of intervention	Results
Harsch et al. (2004)	Observational	9	OSA + DM	3 months	No significant changes in HbA1c ((mean ± SD) 6.3% ± 0.7% to 6.3% ± 0.6%)
Babu et al. (2005)	Observational	25	OSA + DM	83 ± 50 days (mean ± SD)	Significant reduction in HbA1c in patients with a baseline HbA1c >7%
West et al. (2007)	Randomized controlled	19 CPAP 21 sham	OSA (4% ODI >10) + DM	3 months	No significant changes in HbA1c
Dawson et al. (2008)	Observational	20	OSA + DM	41 days (range 26–96 days)	No significant changes in HbA1c
Steiropoulos et al. (2009)	Observational	56	Nondiabetic OSA (AHI ≥5)	6 months	Significant reduction in HbA1c in patients with mean CPAP use ≥4 h
Smura et al. (2011)	Observational	6	OSA + IGT	2 months	No significant changes in HbA1c
Sharma et al. (2011)	Randomized controlled	43 (CPAP/sham) 43 (sham/CPAP)	OSA	3 months	Significant reduction in HbA1c
Shpirer et al. (2012)	Observational	30	OSA without known DM	3–5 months	Significant reduction in HbA1c

CPAP: continuous positive airway pressure, HbA1c: hemoglobin A1c, OSA: obstructive sleep apnea, DM: diabetes mellitus, ODI: oxygen desaturation index, AHI: apnea–hypopnea index, IGT: impaired glucose tolerance.

to 6.28% ± 0.51%, $p = 0.038$). In contrast, Dawson et al. (2008) found no significant change in HbA1c levels after an average of 41 days of CPAP treatment in 20 diabetic patients with OSA. However, in that study, a significant decrease in the mean 24-h glucose level, measured by a continuous glucose monitoring system, was observed after CPAP treatment. Since an average day of CPAP use was 41 days in that study, it is a possibility that longer-term treatment with CPAP would have led to a significant decrease in HbA1c levels. Results of two other observational studies with a small sample size (<20 patients) (Harsch et al., 2004; Smurra et al., 2011) found no significant changes in HbA1c levels in diabetic patients with OSA. Thus, the results of the previous six observational studies with regard to the effect of CPAP on glycemic control are inconsistent.

In a randomized placebo-controlled study including 42 diabetic males with OSA, West et al. (2007) found no significant differences in changes in HbA1c levels between 19 patients with 3-month treatment with CPAP and 21 patients with 3-month treatment with sham CPAP. However, in that study, the average CPAP use was only 3.3 h/day, and 26% of the CPAP group had CPAP use of <1 h/day. Therefore, poor compliance with CPAP might have led to the negative result. In another randomized placebo-controlled study with a cross-over design, Sharma et al. (2011) found that 3-month treatment with CPAP was associated with a significant HbA1c reduction in patients with moderate-to-severe OSA (absolute changes (mean ± SD): 0.03% ± 0.42% in the CPAP group vs 0.19% ± 0.49% in the sham CPAP group, $p = 0.003$). Furthermore, patients with CPAP use of ≥5 h/day had a significantly greater reduction in HbA1c levels than the whole study population. Thus, the results from the two randomized controlled studies with regard to the effect of CPAP on glycemic control are also inconsistent.

In summary, it is still a matter of debate as to whether treatment with CPAP improves glycemic control in diabetic patients with OSA. The differences in the methodology, sample size, patient selection, duration of treatment with CPAP, and time of CPAP use are thought to be responsible for the inconsistent results among previous studies. Further randomized placebo-controlled studies with a sufficient power are needed to determine the true effect of CPAP on HbA1c levels in diabetic patients with OSA. In such research, we have to keep in mind that long-term treatment with sham CPAP cannot be ethically justified in patients with severe OSA.

MECHANISMS FOR THE ADVERSE EFFECT OF OSA ON GLUCOSE METABOLISM

OSA-induced intermittent hypoxemia (intermittent hypoxemia/reoxygenation) and sleep fragmentation/loss can exert adverse effects on glucose metabolism through several mechanisms. The mechanisms include the effects of hypoxemia (Iiyori et al., 2007), oxidative stress (Zhan et al., 2005), sympathetic nervous activation (Somers, Dyken, Clary, & Abboud, 1995), the dysregulation of the hypothalamic-pituitary-adrenal axis (Vgontzas et al., 2007) and alterations in proinflammatory cytokines such as interleukin-6 and tumor necrosis factor-α (Lavie, 2003). Intermittent hypoxemia may also impair glucose metabolism through apoptosis of pancreatic beta-cells (Xu, Long, Gozal, & Epstein, 2009; Yokoe et al., 2008). These adverse effects on glucose metabolism would increase HbA1c levels in patients with OSA.

DM is a two-step process characterized by insulin resistance and subsequent impaired insulin secretion. Insulin resistance usually begins many years before the onset of DM as a result of interaction of genetic and environmental factors. When insulin secretion is no longer sufficient to overcome insulin resistance, glucose intolerance progresses to DM. Treatment of OSA may improve insulin resistance and maintain the secretory function of pancreatic beta-cells in diabetic patients with OSA. Considering the adverse effects of OSA on glucose metabolism, treatment of OSA may be more effective in the prediabetic phase or in the early phase of DM than in the advanced phase of DM, in which an abundant loss of functioning pancreatic beta-cells is highly likely to exist.

CONCLUSIONS

Numerous studies have shown an independent association between OSA and impaired glucose metabolism, but a causal link between the two conditions remains to be investigated. Previous cross-sectional studies also have shown a positive association between OSA severity and HbA1c levels in nondiabetic and diabetic patients with OSA. However, the effect of CPAP on HbA1c levels in diabetic patients with OSA is inconsistent among previous studies. Considering a high prevalence of OSA in diabetic patients, the clarification of the true effect of CPAP on HbA1c levels in diabetic patients with OSA will have an important implication in the management of DM. Because HbA1c levels have been shown to be associated with mortality and/or cardiovascular events in diabetic and nondiabetic subjects, an OSA-induced increase in HbA1c levels may be involved in the pathogenesis of cardiovascular diseases in patients with OSA. Therefore, it is clinically meaningful to clarify the exact association between OSA and HbA1c levels in diabetic and nondiabetic patients with OSA.

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Part V

Aging and Sleep Deprivation

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Chapter 25

Restless Legs Syndrome (Willis–Ekbom Disease) and Gastrointestinal Diseases

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INTRODUCTION

More than 50 diseases, disorders, and conditions have been reported to be associated and/or contribute to restless legs syndrome (RLS) (recently renamed Willis–Ekbom disease) (Weinstock, Walters, & Paueksakon, 2012). Most of these states have the potential to have systemic inflammation or immune disorders (Weinstock et al., 2012). In addition, in many of these idiopathic syndromes and diseases, there is an underlying gut dysfunction with subsequent dysbiosis and/or small-intestinal bacterial overgrowth (SIBO) (Weinstock, 2011, chap. 11). Recently, idiopathic or primary RLS has been shown to be associated with SIBO, and preliminary evidence suggests that treating the underlying gastrointestinal (GI) disorder can improve RLS severity (Weinstock, 2010).

GI dysfunction is the presence of abnormal metabolic function, motility, structure, infection, or inflammation. Several GI diseases have systemic symptoms and extraintestinal manifestations that may be an expression of such dysfunction. Systemic inflammation resulting from asymptomatic gut dysfunction, including autoimmune phenomenon and increased intestinal permeability (Weinstock, 2011, chap. 11), can lead to extraintestinal disorders.

Examples of extraintestinal manifestations of celiac disease include thyroid disease, liver disease, and osteoporosis (Reilly, Fasano, & Green, 2012). Neurological disorders associated with celiac disease include RLS, peripheral neuropathy, ataxia, migraines, seizure, peripheral neuropathy, cerebellar ataxia, autonomic dysfunction, myopathy, infantile hypotonia, developmental delay, learning disorders, attention-deficit/hyperactivity disorder, occipital calcifications, seizures, and migraines (Weinstock, Walters, Mullin, & Duntley, 2010). Examples of extraintestinal manifestations of inflammatory bowel disease (including Crohn's disease (CD) and ulcerative colitis) primarily consist of arthralgias, erythema nodosum, iritis, and hepatobiliary diseases (Hou, El-Serag, & Thirumurthi, 2009). Neurological disorders associated with CD include RLS and peripheral neuropathy (Weinstock, Bosworth, et al., 2010).

In this chapter, all GI diseases and disorders that are associated with RLS are reviewed (Table 1), and potential mechanisms to explain the relationships are discussed. In the setting of these GI diseases and in primary RLS, the hypothesis for potential food triggers and mechanisms of action of these triggers is proposed. In addition to the GI disorders, 10 other secondary RLS disorders have been linked to SIBO and immune and inflammatory processes (Weinstock et al., 2012). These conditions include Parkinson's disease, diabetes, end-stage renal disease, rheumatoid arthritis, fibromyalgia, scleroderma, pregnancy, hypothyroidism, acromegaly, and advanced age.

Modulation of Sleep by Obesity, Diabetes, Age, and Diet. http://dx.doi.org/10.1016/B978-0-12-420168-2.00025-9

TABLE 1 Iron Deficiency, SIBO, and Inflammatory and/or Immunological Alterations in Gastrointestinal Conditions Associated with RLS

Disease/Condition Associated with RLS	Association with Iron Deficiency[a]	Association with SIBO	Association with Inflammatory and/or Immunological Alterations/ Response[b]
Gastric resection (Banerji & Hurwitz, 1970)	Yes (Ruz, Carrasco, Rojas, et al, 2009; Vargas-Ruiz, Hernandez-Rivera, & Herrera, 2008)	Yes (Murawa, Murawa, Oszkinis, & Biczysko, 2006)	NS
Chronic liver disease (Franco et al., 2008)	Yes (Morgan, Kelleher, Walker, & Losowsky, 1976)	Yes (Lakshmi, Ghoshal, Kumar, et al, 2009)	Yes (Kugelmas, Hill, Vivian, Marsano, & McClain, 2003)
Irritable bowel syndrome (Weinstock, Fern, & Duntley, 2008)	No (Weinstock et al., 2008)	Yes (Mann & Limoges-Gonzales, 2009; Pimentel, Chow, & Lin, 2000; Weinstock et al., 2008)	Yes (Macsharry, O'Mahony, Fanning, et al, 2008; Ohman, Isaksson, Lindmark, et al, 2009)
Celiac disease (Weinstock, Walters, Mullin, & Duntley, 2009)	Yes (Manchanda, Davies, & Picchietti, 2009)	Yes (Rubio-Tapia, Barton, Rosenblatt, & Murray, 2009)	Yes (Fornari et al., 1998)
Crohn's disease (Weinstock et al., 2010)	Yes (Bergamaschi, Di Sabatino, Albertini, et al, 2010; Vijverman, Piront, Belaiche, & Louis, 2006)	Yes (Rutgeerts, Ghoos, Vantrappen, & Eyssen, 1981)	Yes (Mahida, Kurlac, Gallagher, & Hawkey, 1991; Gross, Andus, Caesar, Roth, & Scholmerich, 1992)

NS, not studied; RLS, restless legs syndrome; SIBO, small-intestinal bacterial overgrowth.
[a]*Includes alterations in iron and ferritin levels.*
[b]*Includes alterations in inflammation (changes in interleukins 1, 6, 8, 12, and 17 and tumor necrosis factor-α) and overall immune function.*

GENERAL DISCUSSION OF SMALL-INTESTINAL BACTERIAL OVERGROWTH

The colon is accustomed to having contact with 100 trillion bacteria, yet the small intestine has few by comparison. Complications arise when the coliform count increases in the small intestine or there is an imbalance of bacteria in the colon with harmful bacteria (dysbiosis). The natural protective mechanisms that keep the small-bowel bacteria colony counts suppressed include the presence of stomach acid, normal GI motility, digestive enzymes, mucosal immunity, and the integrity of the ileocecal valve. The balance in the colon is generally kept in check by the background of healthy bacteria, mucosal integrity, and normal motility (Weinstock, 2011, chap. 11).

The SIBO is defined as the presence of more than 10^5 colony-forming units per milliliter in the jejunum with symptoms or signs of bacterial overgrowth or malabsorption. Noninvasive diagnostic testing to determine the presence of SIBO are lactulose or glucose breath tests that determine excess products of fermentation (hydrogen or methane) from the proximal small intestine, which pass into the respiratory system. This condition can result in gas, bloating, flatulence, altered bowel function, and/or malabsorption of nutrients. Bloating, diarrhea, and nutrient deficiencies are induced by excess intraluminal small-intestinal bacteria, which result from the following: (1) fermentation of nutrients producing gas and (2) bile salt deconjugation by bacteria, leading to fat malabsorption and subsequent steatorrhea and secretory effects, causing diarrhea. Bacterial overgrowth is associated with many complex syndromes, including irritable bowel syndrome (IBS), fibromyalgia syndrome, rosacea, interstitial cystitis, and type III chronic prostatitis (Weinstock et al., 2012). Furthermore, SIBO occurs in the setting of many diseases and treatment with antibiotic therapy is beneficial, including RLS (Weinstock, 2011, chap. 11; Weinstock et al., 2008; Weinstock, Walters, Duntley, Zeiss, & Lewis, 2009; Weinstock, 2010).

Chronic SIBO can result in systemic inflammation (Lin, 2004). Circulating levels of cytokines, such as tumor necrosis factor-α and proinflammatory interleukins and immune complexes, are elevated in both SIBO and IBS (Hughes et al., 2013). Net effects of damaged tight junctions of intestinal mucosal cells include stimulation of the inflammatory network and activation of lymphocytes and mast cells locally and systemically. With increased intestinal permeability, there is translocation of lipopolysaccharides (the outer covering of Gram-negative bacteria) into the damaged mucosal lining, which can increase hepcidin production by the liver (Ganz, 2003), which may play a role in RLS.

GASTROINTESTINAL DISEASES ASSOCIATED WITH RLS

Gastric Resection

In 1960, Ekbom reported an increased incidence of RLS in patients who had gastric surgery, which was confirmed by a study among 106 patients with "malabsorption syndrome" after gastric surgery (Banerji & Hurwitz, 1970). The incidence of RLS was 11% in this case series compared with others who had RLS (17% with diabetes, 17% with uremia, and 2% of otherwise healthy individuals). In the 12 post-gastric surgery RLS patients, only three had additional neurological disorders. There was not an apparent correlation of having low iron levels in those affected by RLS versus those without RLS in the total group. Reduced acid production and intrinsic factor production by loss of the antrum and its parietal cells result in decreased iron and vitamin B12 absorption (Koike et al., 2001). Lower levels of ferritin could have been present in this cohort, which can precipitate RLS (Sun, Chen, Ho, Earley, & Allen, 1998), but this particular measurement was not performed. In addition, gastric resection with subsequent achlorhydria and gastroparesis occur, and they promote SIBO, which may have factored into RLS in this group (Paik et al., 2011).

Ulcer surgery has been uncommonly used with the advent of proton pump inhibitors and treatment for *Helicobacter pylori*. We are faced with patients who undergo bariatric surgery, and studies for RLS may prove to be interesting because outcome of surgery has similar malabsorption potential (Vargas-Ruiz, 2001).

Chronic Liver Disease

One of the first published reports of liver disease and RLS is a cohort of patients with hepatitis C (Gemignani et al., 1997). The proposed theory to explain this association was that peripheral neuropathy from cryoglobulinemia caused RLS in these patients.

Two studies subsequently examined the prevalence of RLS in chronic liver disease patients in liver clinics in Chicago (IL) and Japan. The problems interpreting these data include that there was a mixed group of liver conditions in both studies: one study lacked control of other underlying secondary RLS factors, and both did not have age- and sex-matched controls.

In the Chicago tertiary hepatology clinic, investigators used a survey of RLS symptoms on the basis of the International RLS Study Group and its five key questions to determine prevalence of RLS (Franco et al., 2008). Of 141 surveys, 88 (62%) were positive for RLS in this population. RLS risk factors were further assessed through a medical record review. Most of the RLS patients had secondary risk factors, including kidney disease, anemia, iron deficiency, RLS-associated medications, and self-reported neuropathy. Idiopathic or unexplained RLS symptoms had a prevalence of 16.3% (95% confidence interval, 10.6–23.5%). Severity of the liver dysfunction, including the presence of cirrhosis, did not correlate with the prevalence of RLS. The presence of RLS in the affected patients resulted in significantly diminished quality of life. These authors suggested that an increase in central nervous system serotonin precursors in liver disease patients results in dysfunction of the corticospinal tracts, which leads to RLS.

In the Japanese liver disease clinic study, investigators examined the influence on sleep and quality of life and the prevalence of RLS in 149 consecutive patients with chronic liver disease (Matsuzaki et al., 2012). The same questionnaire was used as the Chicago study for a diagnosis of RLS. All cases with any sleep disturbance were evaluated using the Japanese version of the Pittsburgh Sleep Quality Index (PSQI), and health-related quality of life was evaluated by the Japanese Short Form-36 Health Survey. Of 149 patients, 25 (16.8%) fulfilled the diagnostic criteria for RLS. The median global PSQI score of the RLS group was significantly higher than the non-RLS group (9 versus 5; $P<0.01$). In patients deemed poor sleepers (global PSQI score, >5) in the RLS group, the score was significantly higher than in the non-RLS group ($P<0.05$). The mental component summary score of the RLS group was significantly lower than in the non-RLS group.

Neither of the previously described publications tested for neuropathy and SIBO. Peripheral neuropathy is common in chronic liver disease patients, and this may account for many cases of RLS. In a recent study of patients on a liver transplantation waiting list, 65% had peripheral neuropathy (Cocito et al., 2010). Other mechanisms of action that could explain RLS in liver disease include SIBO and/or systemic inflammation, including increased levels of IL-6 and tumor necrosis factor-α, immune changes, and increased hepcidin levels, which occur in liver disease (Schnabl, 2013).

Irritable Bowel Syndrome

The IBS was first recognized to be associated with RLS in 2008 (Weinstock et al., 2008). In 254 IBS patients screened at a community gastroenterology practice for bacterial overgrowth and RLS, 54% had SIBO; of these patients, 13 with RLS were identified. Some of these patients had a history of antecedent gastroenteritis before developing both IBS and RLS. By using a nonabsorbed gut-specific antibiotic (rifaximin), followed by prokinetic drug therapy for the small intestine, 10 (77%) of 13 patients had ≥80% long-lasting improvement of RLS.

In an epidemiological study, 30 patients with diarrhea-predominant IBS, 30 with constipation-predominant IBS, and 30 with mixed-symptom IBS were evaluated for the prevalence of RLS (Basu, Shah, Krishnaswamy, & Pacana, 2011). The diagnosis of RLS was assessed via the

International RLS questionnaire and polysomnography. Twenty-six patients with IBS of all bowel types (29%) were diagnosed with RLS using the RLS questionnaire. Of the 26 patients, 24 (92%) underwent polysomnography and all had RLS confirmed. Patients with RLS were more likely to have diarrhea-predominant IBS (62%) compared with constipation-predominant IBS (4%) or mixed-symptom IBS (33%). In other IBS studies when diarrhea-prone IBS groups are compared with other groups, there is more inflammation diagnosed in the setting of diarrhea.

A study of primary RLS patients addressed the incidence of IBS and SIBO compared with controls (Weinstock & Walters, 2011). RLS subjects were recruited from unbiased advertisements that did not mention GI symptoms. General population controls (GPCs) were spouses of patients who came to a GI clinic, and they were excluded for RLS. Completely healthy controls (CHCs) were excluded for RLS, GI symptoms, and any other disease. The study included 32 RLS subjects (23 females and 9 males; aged 57 years), 25 GPCs (13 females and 12 males; aged 58 years), and 30 CHCs (19 females and 11 males; aged 44 years). Twenty-nine of the RLS subjects had RLS unassociated with other GI diseases, one had celiac disease, and two had gastric resections. IBS was diagnosed in 28% of RLS subjects compared with 4% of GPCs ($P=0.0317$). SIBO was diagnosed in 69% of RLS subjects compared with 28% of GPCs ($P=0.0033$) and 10% of CHCs. By using a false-positive rate of 10%, 59% of positive LBT results are associated with RLS. Four of these patients had IBS that began before onset of RLS symptoms (range, 2–13 years before RLS). In addition, three patients had concurrent onset of RLS and IBS symptoms, and one patient developed IBS 20 years after the beginning of RLS. There seemed to be no relationship between dopaminergic use and IBS. There was no association between RLS severity or duration and the presence of IBS, and neither age nor sex played a role in the distribution of IBS. Thus, in this small study, it appeared that primary RLS patients had an increased incidence of both SIBO and IBS.

Immunological disorders associated with excess gut bacteria (Rubio-Tapia et al., 2009; Rutgeerts et al., 1981) and immunity and inflammation (Mahida et al., 1991) may hypothetically predispose patients to RLS because of effects on central or peripheral nerves. An alternate explanation may be that inflammation leads to iron deficiency with increased hepcidin levels as an intermediary, as has been documented in the literature (Ganz, 2003). Establishing the link between RLS and SIBO may provide a new approach to the treatment of RLS. Current treatments for SIBO, including antibiotic and probiotic therapies, low carbohydrate diet, and stimulation of small-intestinal activity, may be beneficial for patients with RLS. Therapy with the nonsystemic antibiotic rifaximin is emerging as a promising therapy for SIBO and IBS and may be useful as a primary or adjunctive therapy in patients with RLS (Weinstock et al., 2009; Weinstock, 2010). A study is currently underway looking for specific antibodies against invasive bacteria and examining the presence of these antibodies in brain and peripheral nerve tissue in healthy individuals and patients with RLS to solidify the association between inflammation and RLS.

Celiac Disease

Celiac disease is a common autoimmune disease (affecting 1 of 133 people in the United States) and is associated with many neurological disorders by different mechanisms (Green et al., 2005).

Celiac disease was investigated as a potential cause for iron deficiency in four consecutive patients with RLS and a ferritin level of <25 ng/mL (Manchanda et al., 2009). Mild anemia was present in only one of these four patients. All were confirmed to have celiac disease by duodenal biopsy, and they responded to a gluten-free diet. Marked improvement in RLS symptoms occurred in all, and the two patients who were taking medications were able to stop therapy. In two cases, response to gluten was independent of the iron level: one had rapid improvement on the gluten-free diet before seeing the ferritin level increase, and the other had relapses in RLS with dietary noncompliance.

A survey study was performed of celiac patients compared to the spouse controls to determine the incidence and prevalence of RLS (Weinstock et al., 2010). The incidence of RLS among 85 patients with celiac disease was 35%, with a prevalence of 25% compared with 10% of spouses ($P<0.02$). In 79% of the patients with RLS and celiac disease, RLS symptoms began during or after onset of the GI symptoms. A prospective evaluation of iron deficiency was determined in those with active RLS. Iron deficiency was present in 40% of the celiac patients with active RLS compared with 6% of patients who never had RLS ($P<0.001$). After 6 months of a gluten-free diet, RLS symptoms improved in 50% of 28 patients. Secondary RLS conditions other than iron deficiency were uncommon in the patients with and without RLS. A review of family histories revealed prevalence of RLS in a first-degree relative of approximately 20% in both patient groups. One patient with RLS had a first-degree relative with both celiac disease and RLS. A similar proportion of patients with RLS took selective serotonin reuptake inhibitors (SSRIs) (7%) compared with patients without RLS (9%), and use of SSRIs did not appear to have an effect on RLS symptoms. One patient without RLS who also had Parkinson's disease took dopaminergic medication. The RLS went undiagnosed and untreated in patients for an average of 6 years. Patients with RLS had their celiac disease diagnosed for a mean of 6 years but recalled having GI symptoms for an average of 14 years before a formal diagnosis. This study suggests that celiac disease is frequently associated with RLS and that treatment

with a gluten-free diet, aggressive replacement of iron, or antibiotic treatment of bacterial overgrowth may improve the quality of life in patients with celiac disease who have RLS. Thus, celiac disease may be an underlying correctable factor for some patients diagnosed with idiopathic RLS.

Another investigation of the prevalence of RLS in celiac disease included a population of 100 adult celiac patients and compared them to 100 age- and sex-matched controls in the general population (Moccia et al., 2010). The patients came from a GI clinic that referred them directly and consecutively to the neurology clinic. The authors found a 31% prevalence of RLS in the celiac population, and this was significantly higher than the prevalence in the control population (4%; $P<0.001$). The severity of the patients with RLS was moderate (International RLS Scale score, 17 ± 6.5). In the celiac population, hemoglobin levels were significantly lower in celiac patients with RLS than without RLS (11.8 versus 13.0; $P=0.003$). In celiac patients with RLS, 16 of the 31 were compliant with the gluten-free diet, which did not differ from the celiac patients without RLS. Similarly, there was no difference in ferritin levels (30 versus 36 ng/mL). They excluded correlations between RLS and other possible causes of secondary RLS, including signs of peripheral neuropathy, pregnancy, end-stage renal disease, and pharmacological treatments.

Screening for celiac disease in patients with idiopathic RLS may have importance because celiac disease is a commonly overlooked silent disease. A larger controlled study attempted to answer the question of whether celiac disease is more prevalent in patients with RLS. To determine this, 96 RLS patients and 97 healthy controls, both with or without iron deficiency, were studied (Cikrikcioglu et al., 2010). All secondary causes of RLS, except iron deficiency, were excluded. Tissue transglutaminase antibodies, endomysium antibodies, and gliadin antibodies were tested. In RLS patients, positivity rates of all celiac antibodies were similar to those in controls. However, the rate of iron-deficiency anemia in RLS patients with at least one positive celiac antibody was significantly higher than that of RLS patients whose antibodies were all negative. Overall, the prevalence of celiac antibodies in the RLS patients studied was not increased. These authors suggested that iron deficiency is the key mechanism for RLS in celiac patients.

In contrast, peripheral iron deficiency was not highly correlated with RLS in the two RLS prevalence studies of celiac patients (Weinstock et al., 2010, Moccia et al., 2010). Thus, more than one mechanism (e.g., inflammatory and/or immunological alterations) may be a relevant cause of RLS in celiac disease.

Crohn's Disease

CD is a chronic, inflammatory disease of the GI tract that primarily affects the small intestine and colon. The etiology of CD is not fully understood but most likely results from abnormal mucosal immune responses stimulated by intestinal bacteria in genetically susceptible individuals (Baumagard & Carding, 2007). Both CD and RLS have been associated with inflammation and bacterial overgrowth in the GI tract (Sartor & Muehlbauer, 2007; Biancone, Vernia, Agostini, Ferrieri, & Pallone, 2000). Extraintestinal manifestations of CD have not previously included the central nervous system. Up to a fourth of CD patients get extra intestinal manifestations.

In a prospective multicenter study, RLS was a comorbid condition in 272 CD patients, with an incidence of 43% and a prevalence of 30% (Weinstock, Bosworth, et al., 2010). In this study, the 9% prevalence of RLS in the spouse control group was comparable to the prevalence in the general population. The symptoms of RLS occurred during or after the onset of CD symptoms in most patients, suggesting a link between CD and RLS. There was no difference between the CD groups with respect to current iron deficiency or RLS family history. In 91.8% of patients with RLS and CD, RLS started during or after the onset of CD diagnosis. Among 73 patients with RLS, 67 (44.5%) stated there was a relationship between qualitative RLS symptom improvement with overall CD symptom improvement.

Patients with CD and RLS were significantly older and less likely to have CD of the colon vs patients with CD but not RLS. A primary risk factor of RLS, genetic predisposition, was assessed as the incidence of RLS in a first-degree relative and was not significantly different among patients with CD with or without RLS (12.0% for both groups). Although RLS symptoms in patients with CD were not associated with current history of iron deficiency (4.6% versus 4.7% for patients with and without RLS symptoms, respectively), the percentage of individuals with iron deficiency in the past was significantly higher in patients with CD and RLS than in patients with CD without RLS symptoms (49.3% versus 33.1%; $P=0.031$). Other secondary RLS risk factors were not significantly different between patients with CD with or without RLS symptoms. The pathophysiology of CD includes SIBO and systemic inflammation. The results in the current study suggest ileal involvement in patients with CD may be a risk factor for RLS.

In the previously described study, the incidence of RLS was greater than the incidence of many of the known extraintestinal manifestations of CD, including disorders of the skin, joints, eyes, and liver. The inflammatory state associated with SIBO and CD stimulates proinflammatory cytokines. Proinflammatory cytokines, such as interleukin 6, have increased production of a small peptide, hepcidin, which affects iron transport in in vitro models and in healthy human volunteers (Nemeth et al., 2004). We hypothesize that inflammation in CD, caused by bacterial overgrowth, increases hepcidin levels. This could result in an iron deficiency in the central nervous system, causing RLS.

DIETARY TRIGGERS FOR RLS AND FOR RLS ASSOCIATED WITH CELIAC DISEASE AND SIBO

Studies on RLS food triggers are limited. There are many barriers and defensive mechanisms by which the intestinal tract mucosa can be exposed to antigens, bacteria, and chemicals, yet still be selective about what is absorbed and secreted. Healthy commensal bacteria play a role in protecting the mucosal barrier by directly and indirectly improving immune function. When this balance is disturbed, absorption of food antigens may be increased. When the bacterial load is increased in SIBO, carbohydrate consumption results in increased fermentation, increased bacterial colony counts, and increased inflammation. Gluten sensitivity without celiac disease is a common condition, but it is not known if it can directly affect RLS as it could in those with celiac disease (Jackson, Eaton, Cascella, Fasano, & Kelly, 2012).

According to a posting on the RLS Foundation Website, many with RLS have found alcohol consumption, especially in the evening hours, can lead to an increase in RLS symptoms. Alcohol as a factor for poor sleep was not supported by one epidemiologic study of various sleep disorders, including RLS (Vinson et al., 2010). In contrast, one of us (L.B.W.) has RLS patients who have RLS and concomitant SIBO who have exacerbations of RLS symptoms by alcohol intake. This may relate to fructose consumption, and this will be addressed later in this section. The effect of alcohol on periodic limb movements was evaluated in 40 alcohol-dependent patients (Gann et al., 2002). Alcohol-dependent patients displayed a significantly enhanced periodic limb movement syndrome (PLMS) arousal index compared to age- and sex-matched healthy subjects. The PLMS-arousal index was significantly elevated in patients who relapsed during the next 6 months compared to abstinent patients. The study did not address RLS per se.

In another posting on the RLS Foundation Website, it was stated that many with RLS have found that caffeine leads to an increase in RLS symptoms. A clinical, uncontrolled study of 62 RLS patients and associated anxious-depressed states suggested that caffeine worsened RLS symptoms (Lutz, 1978).

Saccharin as an additive has been studied and was compared to cyclamate in a randomized, double-blind, placebo-controlled trial with a crossover design (de Groot, 2007). During a period of 48 days, the subjects took four capsules per day containing either 150 mg of cyclamate or 22.5 mg of saccharine, either sweetener or placebo, on 2 successive days. Between each of these 2-day periods, there was a 2-day rest period during which no capsules were taken. The subjects had symptoms more often and more severe while using saccharine or the combination of saccharine and cyclamate than when taking the placebo. The potential mechanism of action is unknown.

In one of the antibiotic treatment studies for bacterial overgrowth in RLS, an observation was made that consumption of alcohol and fruit exacerbated RLS symptoms (Weinstock, 2010), and other clinic patients have had similar problems. Foods high in carbohydrates or carbohydrates that are difficult to digest, such as the "FODMAPs," should be examined. These foods are substrates for bacterial fermentation and, hence, could not only explain worsening symptoms in patients with IBS but also those with SIBO and possibly SIBO-associated RLS. The term FODMAPs stands for fermentable oligosaccharides, disaccharides, and monosaccharides and polyls. These include lactose, fructose, fructans, galactans, and sugar alcohols. Fructans are present in wheat, onions, garlic, and other vegetables.

CONCLUSIONS

Common GI diseases and disorders, including IBS, celiac disease, CD, and chronic liver disease, have a relatively high prevalence of RLS. The prevalence of SIBO and of IBS appears to be increased in patients with RLS, but larger studies will be required to be definitive (Weinstock & Walters, 2011). Although the prevalence of RLS is higher in celiac disease (Weinstock et al., 2010; Moccia et al., 2010), the reverse is not true (i.e., there is not an increased prevalence of celiac disease in RLS patients) (Cikrikcioglu et al., 2010). This is exactly what one would expect if the inflammatory/immunological processes associated with celiac disease lead to RLS and not vice versa. In cases of other GI disorders in which RLS is increased, such as in CD, it is suggested that these reverse prevalences (e.g., the prevalence of CD in RLS) also be investigated. Findings similar to those found with celiac disease would similarly strengthen the immunological hypothesis for the pathogenesis of RLS. Overall and in summary, the pathophysiology of a subset of RLS may relate to underlying GI dysfunction, inflammation, or immune mechanisms.

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Chapter 26

Relationship between Circadian Rhythms, Feeding, and Obesity

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GENERAL INTRODUCTION

Circadian rhythms are nearly 24-h patterns present in nearly all living organisms. It is hypothesized that organisms developed these rhythms as a means of anticipating and adapting to the light–dark cycle in the earth's 24-h day, thus organizing energy production and conservation (Bass, 2012). A fundamental feature of circadian rhythms is that they persist outside environmental cues. External cues such as light and activity can influence the circadian clock and are important factors in entraining the circadian rhythm (Duffy & Wright, 2005; Klerman et al., 1998). In humans, circadian patterns have been demonstrated in body temperature and hormones as well as more complex behaviors such as mood, cognitive performance, and sleep propensity (Czeisler et al., 1999; Dijk, Duffy, & Czeisler, 1992; Dijk, Shanahan, Duffy, Ronda, & Czeisler, 1997). Given the important role that circadian timing has in regulating many of the body's functions, it is not surprising that disturbances in the temporal relationship between feeding and other central and peripheral circadian rhythms could contribute to obesity. The goal of this chapter is to discuss the relationships between circadian disruption in sleep and feeding patterns with obesity risk. This chapter will review data from experimental studies conducted in animal models and humans as well as observation studies in humans linking circadian timing and disruption to dietary behavior and obesity risk.

Circadian Rhythms

The term "circadian rhythm" is derived from the Latin, meaning "about a day," and refers to multiple patterns present in physiology and behavior that occur with a period of about 24 h. These circadian rhythms are present in nearly all organisms, ranging from cyanobacteria and plants to mammals. In humans, circadian rhythms have been observed in body temperature and hormones (e.g., prolactin, melatonin, leptin) as well as more complex behaviors such as cognitive performance, sleep propensity, and appetite. Circadian rhythms are coordinated by the suprachiasmatic nucleus (SCN), which is located in the anterior hypothalamus (Reppert & Weaver, 2001). Because the circadian rhythm is not exactly 24 h, environmental factors such as light, activity, and melatonin are needed to entrain the phase of the circadian rhythm to the 24-h day (Hastings, 1997; Takahashi, 1995). These environmental factors are often called zeitgebers (or "time givers") and without them the circadian clock will free-run (Czeisler et al., 1999). The timing of zeitgebers is important because of the differential effects based on the relative time of administration (Khalsa, Jewett, Cajochen, & Czeisler, 2003; Kripke, Elliott, Youngstedt, & Rex, 2007; Lewy, 2007). Exposure to morning light after the core body temperature minimum (CBTm) will advance (i.e., make earlier) the circadian rhythm, whereas evening light

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before the CBTm will delay the rhythm (Duffy & Wright, 2005; Strogatz, 1990). Production of melatonin by the pineal gland is driven by the SCN (Challet, 2013; Stehle, von Gall, & Korf, 2003). Melatonin receptors are present in the SCN, which has an important role in phase entrainment (Pitrosky, Kirsch, Malan, Mocaer, & Pevet, 1999). Phase shifts with administration of exogenous melatonin are opposite to those of light; i.e., evening melatonin administration results in a phase advance of the circadian clock (Burgess, Revell, Molina, & Eastman, 2010; Lewy, Ahmed, Jackson, & Sack, 1992).

The molecular mechanism of the circadian system has been demonstrated in all human cells. The earliest clock genes were discovered in the fruit fly (*Drosophila melanogaster*) (Konopka & Benzer, 1971). In humans, several clock genes have been identified (e.g., *CLOCK*, *CRY*, *BMAL*) (Lowrey & Takahashi, 2000). These clock genes comprise an autoregulatory transcriptional-translational feedback loop with a 24-h cycle. Circadian rhythms have also been discovered in the periphery, including rhythms in organs (e.g., heart, stomach, liver, lung) and organ systems (e.g., cardiovascular, renal) (Dibner, Schibler, & Albrecht, 2010; Gachon, Nagoshi, Brown, Ripperger & Schibler, 2004). Figure 1 depicts the relationships among SCN, circadian genes, and rhythms of peripheral tissues as well as the metabolic and behavioral outputs. The SCN coordinates these peripheral rhythms through hormonal and neurologic pathways. It is estimated that approximately 10% of all genes in each cell demonstrate rhythmic expression (Panda 2002; Ueda 2002; Hughes 2009).

Rhythms in Feeding Behavior, Hunger, and Appetite

Feeding is another behavior that has been demonstrated to affect circadian rhythms of gene expression as well as behavioral patterns. Feeding behaviors and energy homeostasis are controlled by a complex set of signals (hormonal and nutrient-based) to brain areas including several areas of the hypothalamus (arcuate and ventromedial nuclei) and brainstem (e.g., nucleus of the solitary) as well as inputs to the hypothalamus from reward- and motivation-related signals (Blouet & Schwartz, 2010). One of the most prominent effects of feeding on behavioral rhythms is food anticipatory activity (FAA), which is demonstrated in rodent models. Mice fed during restricted times in the daytime (their typical sleep period) demonstrate awakenings and food-seeking behavior 2–3 h before feeding time. These changes in the rest–activity rhythm are not attributed directly to changes in the central circadian rhythm of the SCN (Boulos, Rosenwasser, & Terman, 1980). Several brain regions have been implicated as being involved in the food entrainable oscillator, but it has not been linked to only one specific area. An output of the SCN to the dorsal medial hypothalamic area is thought to be important to the development of food anticipatory activity (Chou et al., 2003). However, this region does not completely explain FAA, because DMH-lesioned mice have dampened FAA but some FAA activity remains (Acosta-Galvan et al., 2011; Landry, Simon, Webb, & Mistlberger, 2006). Shifting the timing of feeding also affects the relationship between gene expression in peripheral tissues. Shifting to daytime feeding alters the phase

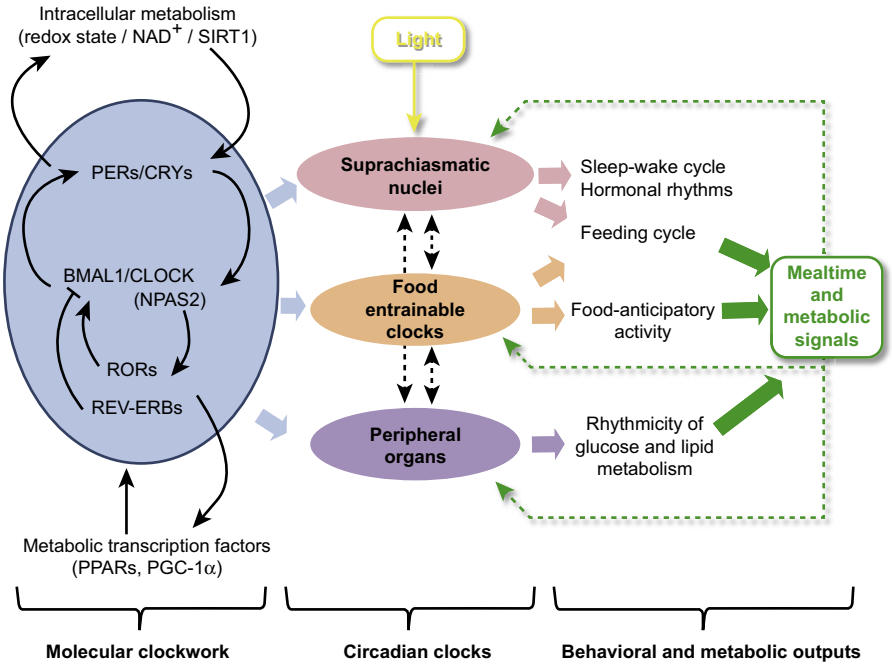

FIGURE 1 Multilevel interactions between circadian clocks and metabolism in mammals. The molecular clock is present in virtually all tissues. The master clock in the suprachiasmatic nuclei and other secondary clock in the brain adjust the phase of behavioral rhythms (sleep–wake and feeding cycles and food-anticipatory activity), whereas peripheral clocks/oscillators participate in the rhythms of metabolic processes (e.g., glucose tolerance, insulin sensitivity, fatty acid oxidation, fat storage). In turn, mealtime cues and metabolic signals feed back on circadian clocks to modulate their oscillations. *Figure reproduced from Challet (2013).*

of gene expression in the liver but not in the SCN (Hara, Lopes Rocha, & Lima-Costa, 2004; Stokkan, Yamazaki, Tei, Sakaki, & Menaker, 2001).

The circadian patterns of hunger and appetite have been investigated in two human studies, with mixed findings, which may be the result of methodological differences between studies (e.g., free choice feeding vs fixed feeding and use of different scales). Both of these studies used a forced desynchrony protocol that allows the evaluation of the circadian effects independently of sleep–wake activities. In this protocol, individuals are scheduled for a 20- or 28-h "day" and sleep–wake behaviors and meals are progressively moved around the clock (Czeisler et al., 1999; Dijk et al., 1992; Kleitman & Kleitman, 1953). This allows researchers to estimate physiologic, psychological, and behavioral processes at different circadian times, while in theory maintaining consistent sleep–wake activity. In a study conducted by Scheer, Morris, and Shea (2013), participants demonstrated a circadian rhythm in hunger, with a trough at what corresponds to about 7:50 AM and a peak at 50°/230° or about 7:50 PM. The circadian effects were independent of time since wake and time since last meal. Rhythms were also present in appetite for salty, sweet, and starchy foods, fruits, meats, food overall, and estimates of how much they could eat, with the lowest point in the morning and highest in the evening (40–60°). The strongest rhythm was demonstrated in self-rated nausea. Interestingly, the desire to eat vegetables and dairy and sensation of fullness did not show a circadian rhythm. An earlier study used a 28-h day and allowed individuals free choice of food (Waterhouse et al., 2004). This study did not demonstrate a circadian effect on meal size or type (e.g., hot or cold). The first meal or breakfast was typically a snack. Lunch and dinner tended to be larger and hot meals. For example, even if "dinner" was occurring at 7:00 AM, participants preferred a large hot meal. These two studies present different approaches to the assessment of the circadian rhythm of appetite and hunger. Together, they suggest that although a rhythm exists for hunger and appetite, social and cultural factors are important in determining meal size and type of foods consumed.

CIRCADIAN DISRUPTION AND OBESITY

In 2005, Turek and colleagues reported on altered metabolic outcomes in the *CLOCK* mutant mouse (Turek et al., 2005). These discoveries led researchers to further investigate the role of circadian rhythms in metabolism and weight regulation. The behavioral and metabolic consequences of circadian misalignment of the sleep–wake cycle for the biological rhythm has also been extensively studied (e.g., phase shifts and forced desynchrony) in both human and animal models. More recently, the role of light exposure in weight management has become of interest. In human studies, naturalistic causes of circadian disruption in humans include shift work, extreme chronotypes, and social jet lag.

Molecular Circadian Disruption and Obesity

The effects of *CLOCK* gene mutations on locomotor activity were first reported in 1994. This was followed by the discovery of the first mammalian circadian gene (*CLOCK*) (King et al., 1997; Vitaterna et al., 1994). It was not until 2005 that Turek and colleagues reported on the altered metabolic outcomes in the clock mutant mouse (Turek et al., 2005). Subsequent research documented that mutations in this gene cause disruptions in sleep homeostasis (Naylor, 2000), eating patterns, glucose regulation, and fatty liver (Turek et al., 2005). Furthermore, alterations in other key genes involved in molecular circadian regulation (e.g., *BMAL* knockout mice) have been associated with weight gain (Shi, Ansari, McGuinness, Wasserman, & Johnson, 2013). In addition to these genetic models, there is recent research that supports a direct role of the SCN in weight and metabolism. SCN-lesioned mice lose circadian rhythmicity of sleep, activity, and insulin sensitivity and demonstrate a small increase in body mass index (BMI) (Coomans et al., 2013). Bidirectional pathways between circadian disruption and obesity have been demonstrated. For example, high-fat diets have been demonstrated to cause phase delays as well as fragmentation of sleep and feeding rhythms (Kohsaka et al., 2007).

In humans, there are at least two studies of human *CLOCK* gene polymorphisms related to body weight and dietary patterns (Garaulet et al., 2009, 2010). The *CLOCK* single nucleotide polymorphism (SNP) *rs3749474* was related to total energy intake among overweight individuals and *CLOCK 3111T→C* genotype was related to saturated fatty acid intake. The animal models strongly demonstrate a critical role of the SCN and circadian genes in weight regulation and glucose metabolism. Less is understood about these relationships in humans, but existing studies support the hypothesis that circadian clock function may be involved in a genetic predisposition to obesity.

Light Exposure

Another potential source of circadian disruption is light at night, which is hypothesized to increase obesity through disruption of circadian rhythms (Fonken, Melendez-Fernandez, Weil, & Nelson, 2014). Several studies demonstrate the effects of light on circadian rhythms, feeding patterns, and obesity risk in animal models. Fonken and colleagues (2009) reported that mice housed in constant bright light gained more weight than mice housed in dim light. Dim light has also been associated with weight gain in mice, compared with mice on a light–dark schedule (Fonken, Aubrecht, Melendez-Fernandez, Weil, & Nelson, 2013).

Further studies of mechanisms replicated the findings by Fonken and colleagues and demonstrated that constant bright light conditions reduce rhythm amplitude, increase food intake, decrease energy expenditure, and eliminate circadian variation in insulin sensitivity (Coomans et al., 2013). Several potential mechanisms of light during the sleep period have been suggested (Bray et al., 2013). Mice fed only during the light phase consumed a large meal upon food availability, consumed more calories per day, and demonstrated a higher respiratory exchange ratio, changes in phase and amplitude of circadian and metabolic genes in certain tissues (e.g., liver), greater weight gain, and diminished amplitude in diurnal variation in humoral factors (e.g., corticosterone).

There is also recent evidence in humans from our group demonstrating that light exposure patterns during the day are associated with differences in body weight. This study found that individuals who obtained most of their daily light exposure at or above 500 lux earlier in the day had a lower body mass index than those who had most of their light exposure later in the day (Reid et al., 2014). This finding is supported by several intervention studies that found that overweight women who were exposed to at least 45 min light between 6 and 9 AM had a greater decrease in body fat compared with those in the dim light control group (Danilenko, Mustafina, & Pechenkina, 2013). Another study that combined exercise and bright light compared with exercise alone found that the whereas both groups of women lost weight, those in the light and exercise condition had a greater decrease in body fat compared with the exercise-alone group (Dunai et al., 2007). There is also evidence that light exposure in the morning may alter the effects of sleep restriction on leptin and ghrelin levels (Figueiro, Plitnick, & Rea, 2012). Specifically, under conditions of sleep restriction, morning light exposure (red, green, and blue wavelengths) significantly increased leptin and decreased ghrelin levels compared with the dim light control, which may counter the increased hunger typically observed with sleep restriction. Although the effects of light on body weight are not well understood, light exposure may influence body weight through the regulation of hormones involved in hunger and satiety.

Human Forced Desynchrony and Phase-Shifting Studies

Misalignment of sleep–wake timing with circadian rhythms has been associated with changes in appetite-regulating hormones and glucose metabolism in human studies. Several of these studies have used temporary phase shifts (Gonnissen, Hursel, Rutters, Martens, & Westerterp-Plantenga, 2012; Gonnissen et al., 2013; Hampton et al., 1996; Schoeller, Cella, Sinha, & Caro, 1997) as well as forced desynchrony to evaluate the effects of circadian disruption on weight regulation and metabolism (Scheer, Hilton, Mantzoros, & Shea, 2009; Wright, Hughes, Kronauer, Dijk, & Czeisler, 2001). One study randomized participants to a forced desynchrony protocol of 24.6-h days or a typical 24-h day for a period of 25 days. In this study, only some participants were able to entrain their circadian rhythm (i.e., shift later each day) and thus accommodate to the longer day (Gronfier, Wright, Kronauer, & Czeisler, 2007; Wright et al., 2001). Participants who were unable to entrain had lower leptin levels during wakefulness, which may predispose individuals to consume more calories. Another study used a 28-h forced desynchrony protocol for 8 days and demonstrated decreased leptin as well as higher glucose despite higher insulin when the sleep–wake schedule was 12 h out of phase with the circadian rhythm (Scheer et al., 2009). These studies demonstrate that misalignment of the sleep–wake cycle to the circadian rhythm has significant implications for processes that affect hunger and appetite, eating behaviors, and weight regulation.

Shift Work

Shift work is one of the leading causes of sleep loss and circadian disruption in the population. Although there is no official definition of shift work, it typically encompasses both overnight and early morning work. It is estimated that 20% of the workforce engages in a shift work schedule. Shift work has been associated with a 1- to 4-h loss in sleep compared with day workers (Akerstedt, 1995; Knauth et al., 1980). In addition, shift workers often experience circadian disruption because of the need to work during the typical sleep period. There have been many studies investigating the negative health effects of shift work, including cardiovascular disease, hypertension, and diabetes (Esquirol et al., 2011). The increased prevalence of obesity among shift workers has been demonstrated in many studies (Antunes, Levandovski, Dantas, Caumo, & Hidalgo, 2010). Cross-sectional associations have demonstrated greater risk for obesity among night factory workers and workers with rotating shifts compared with day workers (Barbadoro et al., 2013; Di Lorenzo et al., 2003). The frequency of shifts worked demonstrated a dose–response relationship with BMI and triglycerides (Karlsson, Knutsson, & Lindahl, 2001). These studies controlled for age and length of employment at the current shift. One study demonstrated shift work to be an independent predictor of weight gain in a longitudinal study (Suwazono et al., 2008).

The mechanisms linking shift work to increased risk of weight gain are broad and are related to a wide range of metabolic and behavioral factors linked to sleep loss and circadian misalignment (Esquirol et al., 2011). Research in both human and animal models has demonstrated some of the deleterious effects of shift work. Animal models of

shift work have also demonstrated that shift work affects behavior, glucose metabolism, and weight gain, as well as alignment between gene expression in the SCN and peripheral tissues. In an early study, rats subjected to twice weekly 12-h phase shifts for 13 weeks demonstrated accelerated weight gain and decreased activity (Tsai, Tsai, Hwang, Huang, & Tzeng, 2005). Another study demonstrated greater weight gain in rats with a 64-day phase shifting protocol compared with a 12-h light–dark schedule despite similar caloric intake (Deibel, Hong, Himmler, & McDonald, 2014). Several studies of simulated shift work experiments in rats forced to walk slowly on wheels during the night (Salgado-Delgado, Angeles-Castellanos, Saderi, Buijs, & Escobar, 2010; Salgado-Delgado et al., 2013). These studies demonstrated that both forced activity and food availability during the rest phase affect alignment between peripheral and central metabolic gene expression.

In human studies, impaired glucose tolerance has been reported among phase shifts in the laboratory as well as in workers starting a new shift (Hampton et al., 1996; Lund, Arendt, Hampton, English, & Morgan, 2001). A study by Buxton et al. (2012) tested the combined effects of sleep restriction (5.6 h of sleep) and circadian disruption (28-h "day"). The combined effect of sleep disruption and circadian misalignment resulted in a decreased metabolic rate and a higher glucose response to meals.

Numerous studies have evaluated dietary behavior in shift workers compared with day workers. Most of these studies demonstrated no difference in 24-h calorie recalls or food diaries between day and shift workers (de Assis, Kupek, Nahas, & Bellisle, 2003; de Assis, Nahas, Bellisle, & Kupek, 2003; Lennernas, Hambraeus, & Akerstedt, 1995; Reinberg et al., 1979). Only one study reported higher caloric intake and fewer meals in late shift workers (Geliebter, Gluck, Tanowitz, Aronoff, & Zammit, 2000). Each published study has reported differences in the timing of food intake between day and shift workers, most notably that shift workers consume calories when day workers are sleeping (de Assis, Kupek, et al., 2003; de Assis, Nahas, et al., 2003; Lennernas et al., 1995; Reinberg et al., 1979). In an in-depth diary study of determinants of food intake among shift workers, Waterhouse, Buckley, Edwards, and Reilly (2003) demonstrated that shift workers' food intake was more influenced by time and availability than hunger, and they reported a greater change in eating behaviors from workdays to free days compared with day workers. They also looked forward significantly less to meals. In summary, eating patterns and determinants of eating behavior are different between shift and day workers. It has been suggested that the pattern of eating, including eating at night and consuming fewer meals, may be associated with weight gain over time.

Chronotype

A growing body of literature also links individuals' preferences for the timing of sleep and wake activities, or chronotype, to dietary behaviors and obesity risk. Being an extreme chronotype may put individuals at risk for short sleep duration and circadian misalignment, owing to the need to conform to the typical work and social schedule. Chronotype has been extensively surveyed in large population studies. These studies have demonstrated that chronotype has a traditional bell-shaped distribution, in which a fraction of individuals are strong morning or evening types but most individuals are intermediate, neither morning nor evening types (Roenneberg et al., 2007). The terms "morningness" and "eveningness" are used to describe where an individual falls in this distribution, with extreme morning types and extreme evening types being at the poles of the distribution. Chronotype is typically measured using self-reported questionnaires, such as the Morningness–Eveningness Questionnaire, Munich Chronotype Questionnaire, and Composite Scale of Morningness (Horne & Ostberg, 1976; Smith, Reilly, & Midkiff, 1989; Zavada, Gordijn, Beersma, Daan, & Roenneberg, 2005). Chronotype changes with age; children and older adults have an earlier chronotype than adolescents and young adults. Some individuals are unable to sleep at the conventional hours needed for a typical work schedule, because their preferred sleep timing is significantly early or late. This contributes to insomnia, daytime sleepiness, or both, and thus interferes with social and occupational activities or quality of life. These individuals are diagnosed with a circadian rhythm sleep disorder, such as advanced sleep phase or delayed sleep phase disorder, according to criteria in the *International Classification of Sleep Disorders*, 3rd Edition (*International Classification of Sleep Disorders*, 2014).

Several studies have demonstrated greater risk for obesity among evening chronotypes. We reported in a sample of intermediate and evening types a correlation between later chronotype and higher BMI (Baron, Reid, Kern, & Zee, 2011). Lucassen et al. (2013) also demonstrated a correlation between chronotype and BMI among a sample of overweight and obese adults with short sleep duration. Only one published study evaluated body composition and chronotype. A study in individuals with bipolar disorder demonstrated an association between evening chronotype and body fat (Soreca, Fagiolini, Frank, Goodpaster, & Kupfer, 2009). There are also few investigations of circadian rhythm sleep disorders and obesity. To date, only one published study evaluated BMI in delayed sleep phase disorder compared with controls. This study found a higher BMI in delayed sleep phase disorder cases compared with age- and sex-matched healthy controls, 33 versus 30 kg/m^2 (Kripke et al., 2008).

Dietary behavior may be a factor leading to higher weight among evening types. Multiple studies have reported that later chronotype is associated with less regularity of lifestyle in general as well as poorer health behaviors overall, including smoking, alcohol, and physical activity (Kabrita, Hajjar-Muca, & Duffy, 2014; Monk, Buysse, Potts, DeGrazia, & Kupfer, 2004; Urban, Magyarodi, & Rigo, 2011). Our lab reported that evening types consume more calories and a larger dinner and have poorer diet quality such as greater frequency of fast food and lower fruit and vegetable consumption (Baron et al., 2011). Similar findings were reported in a survey conducted in young women in Japan (Sato-Mito et al., 2011). One study also reported higher scores on the binge-eating scale in evening chronotypes (Harb et al., 2012). Taken together, these studies demonstrated higher calories and poorer diet quality among evening types.

The specific mechanisms that link chronotype to poorer dietary behaviors are unknown. Evening types may be at increased risk of weight gain owing to circadian misalignment; however, few studies have evaluated circadian markers and linked misalignment to weight regulation or dietary behavior. Multiple studies demonstrate that evening chronotypes have later timing of the circadian markers melatonin and CBT (Baehr, Revelle, & Eastman, 2000; Folkard, Monk, & Lobban, 1979; Waterhouse et al., 2001). Several studies also demonstrated that evening types have differences in alignment between sleep with melatonin and CBT (Duffy, Rimmer, & Czeisler, 2001; Kerkhof & Lancel, 1991; Mongrain, Carrier, & Dumont, 2006). Nonetheless, few studies have linked these measures to obesity risk or dietary behaviors.

Social Jet Lag

The term "social jet lag" is related to chronotype but is conceptually distinct. Social jet lag is defined as the difference in sleep–wake timing between weekdays and weekends (Wittmann, Dinich, Merrow, & Roenneberg, 2006). Individuals have social jet lag because their sleep–wake or social schedule often differs with the sleep–wake schedule needed for the typical work week (Roenneberg et al., 2007; Roenneberg, Wirz-Justice, & Merrow, 2003). Therefore, some individuals must shift their schedule several hours between workdays and free days each week. The need for an alarm clock for most working people is an indication that most individuals would sleep later on free days than on workdays. This frequent shifting is a cause of repeated circadian misalignment and may predispose individuals to poorer health behaviors and weight gain. Individuals with late chronotype often have larger social jet lag owing to the need to conform to the typical schedule during the working week. Social jet lag has been associated with smoking and alcohol and caffeine consumption (Wittmann, Paulus, & Roenneberg, 2010). One study was published that demonstrated an association between social jet lag and BMI only among overweight and obese individuals. There was no relationship between social jet lag and BMI among normal weight individuals (Roenneberg, Allebrandt, Merrow, & Vetter, 2012).

TIMING OF FEEDING

In addition to sleep–wake timing, there is a growing literature demonstrating the importance of the timing of eating in circadian rhythms and weight regulation. These studies demonstrated in animal and humans that the timing of feeding can affect both circadian rhythms and weight regulation. Although there are few experimental models of inappropriately timed eating in humans, surveys of eating patterns or investigations of disorders such as night eating syndrome (NES) provide insight into the deleterious effects of eating at night.

Eating at Night

Studies in animal models suggest that consuming food at the wrong biological time may lead to weight gain independently of caloric intake. Several studies demonstrate that feeding mice during the light period (rest period) causes weight gain (Arble, Bass, Laposky, Vitaterna, & Turek, 2009; Shi et al., 2013). Arble et al. (2009) demonstrated that mice fed a high-fat diet during the light period (rest period) gained twice as much weight as mice fed a high-fat diet during the dark period (active period) (Figure 2). Furthermore, several studies demonstrated that food timing can ameliorate the obesogenic effects of inappropriately timed light or simulated shift work in animals. Restricting food availability to the active phase in mice housed in constant dim light prevents weight gain (Fonken et al., 2010). Salgado-Delgado (2010) also demonstrated that restricting food to the active period prevents obesity and misalignment of central and peripheral rhythms in rats engaged in forced activity during the rest phase.

Furthermore, results suggest that the timing of feeding has an important role in alignment between central and peripheral rhythms. It has been known for some time that changing the availability of food timing shifts the peripheral but not the central clock (Stokkan et al., 2001). Damiola et al. (2000) demonstrated that temporal feeding restriction can shift peripheral gene expression but it did not affect gene expression in the SCN. This study also demonstrated that restricting feeding to only the rest period shifted the rhythm of gene expression in the liver, but feeding ad lib or during the active period did not cause this shift in gene expression.

Night Eating Syndrome

One of the largest bodies of literature about eating at night in humans is from samples of NES. Night eating syndrome is

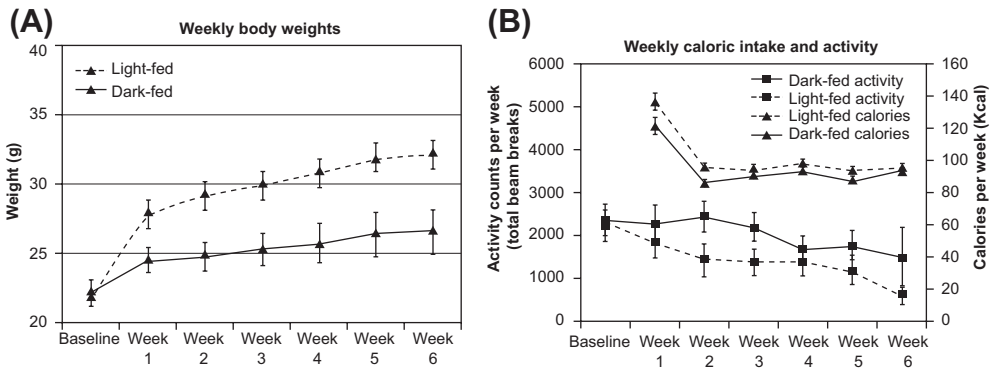

FIGURE 2 Effect of circadian feeding on body weight, caloric intake, and activity. (A) The effect of light or dark phase feeding on body weight. Body weight (mean ± SEM) of C5BL/6J mice fed 60% high-fat only during the 12-h light phase (dashed line) or only during the 12-h dark phase (solid line). Body weight was taken at the end of the 12-h feeding phase in all animals. Within 2 weeks of maintenance on the high-fat diet, the light-fed animals weighed significantly more than the dark-fed animals (*$p < .05$ light-fed vs dark-fed) and remained significantly heavier over the next 4 weeks. (B) Weekly activity counts and caloric intake. Total weekly activity counts (squares) and calories (kcal, triangles) are depicted for both light-fed (dashed line) and dark-fed (solid line) groups (mean ± SEM). Whereas over the 6-week period neither activity nor caloric intake differed significantly ($p > .10$), the light-fed group appeared to be consuming more calories and moving less than the dark-fed group. This raises the possibility that the additive effect of a small increase in caloric intake and a small decrease in activity can together contribute to specific differences in body weight. *Figure reproduced from Arble, Ramsey, Bass, and Turek (2010).*

characterized by evening hyperphagia and nocturnal awakenings in which individuals wake and cannot return to sleep without eating (Stunkard, Allison, Lundgren, & O'Reardon, 2009; Stunkard, Grace, & Wolff, 1955). Numerous studies have reported an increase in weight as well as poor weight loss outcomes among those with NES (Gallant, Lundgren, & Drapeau, 2012). NES has been associated with higher BMI among individuals seeking weight loss (Calugi, Dalle Grave, & Marchesini, 2009) and bariatric surgery candidates (Adami, Meneghelli, & Scopinaro, 1999; Allison et al., 2008; Rand, Macgregor, & Stunkard, 1997). Several studies have reported greater weight gain in those with NES (Andersen, Stunkard, Sorensen, Petersen, & Heitmann, 2004; Marshall, Allison, O'Reardon, Birketvedt, & Stunkard, 2004; Napolitano, Head, Babyak, & Blumenthal, 2001). One study reported that night eating preceded obesity in 40% of obese night eaters (de Zwaan, Roerig, Crosby, Karaz, & Mitchell, 2006). Some studies, but not all, have reported poorer weight loss outcomes in behavioral weight loss programs (Gluck, Geliebter, & Satov, 2001; Stunkard et al., 1955). For example, one study reported lower initial weight loss after bariatric surgery is less in individuals with NES, but similar 5-year weight loss outcomes between individuals with and without NES (Dalle Grave, Calugi, Ruocco, & Marchesini, 2011).

Eating Late, Non-clinical Populations

Eating late has been associated with higher BMI in several studies of adults. Our group reported that consuming more calories after 8 PM was associated with BMI independent of sleep timing and duration (Baron et al., 2011). This result was also demonstrated in an epidemiologic sample. In a study of energy intake in men, obese men had double the energy intake between 10 PM and 4 AM than normal weight men (8% vs 4%) (Andersson & Rossner, 1996). Chronotype was also related to eating late among obese individuals with short sleep duration (Lucassen et al., 2013). Two studies highlighted the potential role of meal timing in weight loss. One reported greater weight loss among individuals who consumed the main meal (Lunch) before 3 PM (Garaulet et al., 2013). Another study from this group reported that women who had a more robust amplitude of circadian rhythms and less fragmentation in their rest–activity rhythm among adults enrolled in a weight loss program had greater weight loss (Bandin, Martinez-Nicolas, Ordovas, Madrid, & Garaulet, 2014).

Only a few experimental studies in humans evaluated potential mechanisms between meal timing and weight gain. Krauchi, Cajochen, Werth, and Wirz-Justice (2002) evaluated 3 days of a single morning or evening carbohydrate-rich meal on CBT, heart rate, and salivary melatonin rhythms and demonstrated that nocturnal melatonin was reduced in the evening meal condition compared with the morning meal. Participants in the morning meal condition showed advanced CBT nadir but dim light melatonin onset was not changed. Morgan, Shi, Hampton, and Frost (2012) evaluated the metabolic effects of morning versus evening meal with high and low glycemic index (GI) foods. They found the lowest insulin sensitivity and greatest glucose response to high-GI foods at the evening meal. There was only one experimental study of meal timing in a weight loss study. Jakubowicz, Barnea, Wainstein, and Froy (2013) conducted an experiment that assigned women with polycystic ovarian syndrome to an isocaloric weight loss diet with a high-calorie breakfast or

high-calorie dinner for 90 days. Participants in the high-calorie breakfast group demonstrated greater insulin sensitivity after the intervention. These studies demonstrate that changing the timing of caloric intake has the potential to influence both circadian rhythms and metabolic processes in humans. Given the well-known circadian rhythm of insulin sensitivity (Van Cauter et al., 1991), it appears that timing of meals may hold promise as an intervention to improve metabolic functioning and weight management, particularly for populations at risk for metabolic disease.

SUMMARY

There is a large and growing literature linking circadian disruption to obesity risk. The timing of sleep and feeding both have substantial roles in the regulation of weight and metabolism. Data from animal models and human studies demonstrate that misalignment of the sleep–wake cycle to the melatonin rhythm affects sleep, feeding behavior, glucose regulation, and appetite-stimulating hormones. In humans, shift work or having a late chronotype may predispose individuals to weight gain through circadian misalignment and through unhealthful dietary patterns. Studies also demonstrate that eating late can itself disrupt circadian rhythms and predispose individuals to gain weight. Currently, there are few studies testing the role of aligning circadian rhythms or manipulating the timing of eating in humans. Animal studies suggest that restricting the timing of eating to the active period, even when subjected to another type of circadian disruption such as simulated shift work or altered light–dark exposure, can mitigate the effects of circadian disruption. Although altering meal timing in free-living individuals is likely to be a difficult task, interventions to improve circadian rhythms may hold promise for complementing or enhancing existing weight regulation strategies.

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Chapter 27

The Effects of Nutrition on Sleep and Sleep Complaints among Elderly Persons

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Chapter Outline

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INTRODUCTION

Sleep has an important role in health and is an important part of human life (Fetveit, 2009). Sleep in elderly people has progressive changes caused by general aging processes (Piani, Brotini, Dolso, Budai, & Gigli, 2004). Sleep disturbance is commonly experienced by older adults (Roepke & Ancoli-Israel, 2010). Age-related alterations in the circadian timing system appear to contribute strongly to sleep problems (Roepke & Ancoli-Israel, 2010). Common sleep disturbances in elderly people are sleep-disordered breathing, periodic limb movement in sleep, restless legs syndrome, rapid eye movement (REM) sleep behavior disorder, insomnia, narcolepsy, and circadian rhythm disturbances (Piani et al., 2004; Roepke & Ancoli-Israel, 2010). Several pharmacologic and nonpharmacological approaches have been used to treat patients with sleep disturbance. Many nutrient variables are associated with sleep disturbance, such as short and/or long sleep duration (Grandner, Jackson, Gerstner, & Knutson, 2013). Herbal therapy may provide an alternative to treat some sleep disturbances.

MECHANISMS OF SLEEP

Regulation of the sleep–wake cycle is complex and involves diverse brain circuits and molecules (Buckley & Schatzberg, 2005). The sleep–wake cycle is explained by homeostatic and circadian processes (Van Dongen & Dınges, 2003). Regulation of sleep and wakefulness is controlled by the homeostatic drive for arousal. The homeostatic regulation of sleep is controlled by the ventrolateral preoptic nucleus (VLPO). The VLPO region contains rapid eye movement (REM) active neurons. Neurons in the VLPO contain inhibitor neurotransmitters such as γ-aminobutyric acid (GABA) and the inhibitory neuropeptide galanin. Adenosine may activate VLPO sleep-active neurons (Morairty, Rainnie, McCarley, & Greene, 2004; Van Dongen & Dınges, 2003). An increase in extracellular adenosine decreases wakefulness and causes sleepiness. The VLPO also provides input to the serotoninergic dorsal and median raphe nuclei and the noradrenergic locus coeruleus. The serotoninergic dorsal raphe nucleus provides a substantial proportion of serotonin innervation to the forebrain. Serotonin (5-hydroxytryptamine, 5-HT) has a facilitatory role in promoting arousal in concert with other neurotransmitters such as noradrenaline and acetylcholine (Ach) (Portas, Bjorvatn, & Ursin, 2000).

The circadian regulation of sleep is controlled by the suprachiasmatic nucleus (SCN) of the hypothalamus. The SCN acts as a biological clock. The circadian clock actively promotes both wake and sleep at different phases of the circadian cycle (Mistlberger, 2005). The SCN regulates arousal through the production of hypocretins

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(orexin) and melanin-concentrating hormone. Daily melatonin secretion is important for the organization of circadian rhythms (Claustrata, Bruna, & Chazot, 2005). The hypocretin (orexin), which is released by the posterior lateral hypothalamus, has several physiological functions in the regulation of behavioral and electrographic arousal (Hungs & Mignot, 2001). The SCN also regulates the daily rhythmic release of glucocorticoids by influencing activity of the hypothalamic–pituitary–adrenal (HPA) axis (Mistlberger, 2005). Changes in the HPA axis with aging are a cause of sleep disturbance. Dysfunction of the HPA axis at any level (CRH receptor, glucocorticoid receptor, or mineralocorticoid receptor) can disrupt sleep (Buckley & Schatzberg, 2005).

NUTRITION AND SLEEP PROBLEMS AMONG ELDERLY PERSONS

Insomnia

Insomnia is the most common sleep disorder among the elderly (Roepke & Ancoli-Israel, 2010). Habitual sleeplessness is classified as insomnia. Insomnia is characterized by difficulty initiating or maintaining sleep and is classified according to frequency, duration (acute vs chronic), and cause (Fetveit, 2009; Souza, Magna, & Reimão, 2002). Chronic insomnia means having symptoms at least 3 nights a week for more than a month (Souza et al., 2002). It may coexist with chronic physical and psychiatric conditions (Roth, Roehrs, & Pies, 2007).

Acute insomnia lasts for a shorter time. The most common type is comorbid insomnia, which is associated with medical conditions such as psychiatric disorders, substance abuse, sleep apnea, or restless legs syndrome. There is no identifiable coexisting disorder in primary insomnia. A number of life changes can trigger primary insomnia, including long-lasting stress and emotional upset (Souza et al., 2002).

Primary and chronic insomnia may be linked to changes in neuroendocrine systems, especially hyperactivity of the HPA axis and excess secretion of adrenocorticotropin-releasing hormone and cortisol (Rodenbeck, Huether, Eckart, & Göran, 2002; Roth et al., 2007). Some researchers reported that abnormal corticotropin-releasing factor (CRF) mediates the hyperarousal seen in primary insomnia. Some researchers think that chemical events in the brain associated with the HPA access also cause release of norepinephrine, which may also disrupt sleep (Rodenbeck et al., 2002; Roth et al., 2007).

Food and Herbal Suggestions for Insomnia

Herb	Rationale
Take These Herbs before Bedtime	
California poppy	• A combination of poppy, passionflower, and valerian promotes sound sleep and beneficial rapid eye movement (REM) sleep (Balch, 2006; Feliú-Hemmelmann, Monsal, & Rivera, 2013). • California poppy promotes calmness of the nervous system and relaxation (Balch, 2006). • It binds GABA receptors and inhibits the 5-HT(1A) receptor (Gafner et al., 2006; Souza et al., 2002).
	Explanations: • California poppy should not be used with sedative drugs (Feliú-Hemmelmann, Monsalve, & Rivera, 2013).
Kava-kava (*Piper methysticum*)	• Kava-kava decreases waking, increases slow-wave sleep, and enhances the intermediate stage situated between slow-wave sleep and paradoxical sleep (Balch, 2006). • There are sedative, anticonvulsive, antispasmodic, and central muscular relaxant effects (Balch, 2006). • Kava-kava binds to GABA receptors and inhibits norepinephrine uptake (Attele, Xie, & Yuan, 2000; Head & Kelly, 2009). • GABA is a neuroinhibitory transmitter (Morairty et al., 2004).
	Explanations: • Kava should not be used with alcohol, Jamaican dogwood, passionflower, alcohol, or L-tryptophan (Meoli et al., 2005).
Hops (*Humulus lupulus*)	• The valerian–hops combination is important in reducing sleep latency, extending slow-wave sleep and quality of sleep (Salter & Brownie, 2010; Antoniades, 2012). • It regulates GABAergic activity (Attele, et al., 2000).
	Explanations: • Hops have an allergenic potential (Spiewak & Dutkiewichz, 2002).

Food and Herbal Suggestions for Insomnia

Herb	Rationale
Melissa officinalis (lemon balm)	• *Melissa officinalis* (lemon balm) is contemporaneously used as a mild sedative and/or calming agent (Cases, Ibarra, Feuillere, Rolle, & Sukkar, 2011; Sarrafi-Zadeh et al., 2012). • It decreases duration of the first REM phase (Cases, Ibarra, Feuillère, Rolle, & Sukkar, 2011). • *Melissa officinalis* inhibits cholinesterase enzymes responsible for GABA degradation (Cases et al., 2011; Feliú-Hemmelmann et al., 2013; Head & Kelly, 2009).
	Explanations: • Do not use with drugs such as benzodiazepines, barbiturates, and antidepressants (Cases et al., 2011).
Passionflower	• It promotes calmness and relaxation (Ngan & Conduit, 2001).
	Explanations: • Interacts with opioid and GABA-benzodiazepine receptors (Attele et al., 2000; Head & Kelly, 2009).
Skullcap	• Skullcap is sedative, nervine, antispasmodic, and anticonvulsant. • Skullcap is commonly combined with hops (Wills & Stuart, 2004).
	Explanations: • Kava and skullcap have been linked to hepatotoxicity (Balch, 2006).
Valerian (*Valeriana officinalis*)	• It improves sleep quality, decreases minutes to falling asleep, and reduces the number of night awakenings (Attele et al., 2000; Salter & Brownie, 2010). • Valerian is traditionally sedative (Meoli et al., 2005). • Valerian binds at A1 adenosine receptors (Meoli et al., 2005). • Increases GABA release and inhibits GABA breakdown; binds to benzodiazepine receptors (Head & Kelly, 2009).
	Explanations: • There appears to be evidence of mild subjective improvement in sleep with valerian, especially when used for 2 weeks or more (Salter & Brownie, 2010; Srivastava, Shankar, & Gupta, 2010).
Chamomile	• Chamomile is sedative and contains flavonoids. • It also binds benzodiazepine (BDZ) and GABA receptors in the brain (Srivastava et al., 2010).
	Explanations: • Chamomile has allergic reactions (Srivastava et al., 2010).
Foods	**Rationale**
In the evening eat bananas, dates, figs, milk, nut butter, tuna, turkey and whole grain crackers, or yogurt (Balch, 2006).	• These foods are high in tryptophan, which promotes sleep (Balch, 2006). • Tryptophan reduces sleep onset latency. • Tryptophan is an essential amino acid that is the precursor of serotonin (Attele et al., 2000; Balch, 2006).
Do not eat large meals within 2 h of bedtime (Balch, 2006).	• A meal consumed close to bedtime is associated with sleep disturbance (Sarrafi-Zadeh et al., 2012).
Avoid caffeine, alcohol, and nicotine 4–6 h before bedtime (Balch, 2006).	• Nicotine is a neurostimulant and causes sleep problems (Balch, 2006; Sarrafi-Zadeh et al., 2012).
Avoid bacon, cheese, chocolate, eggplant, ham, potatoes, sauerkraut, sugar, sausage, spinach, tomatoes, and wine close to bedtime (Balch, 2006).	• These foods contain tyramine, which increases the release of norepinephrine, a brain stimulant (Balch, 2006).
Eat kiwi fruit	• Kiwi fruit contains many medicinally useful compounds, among which antioxidants and serotonin may be beneficial in the treatment of sleep disorders. • Kiwi fruit consumption may improve sleep onset, duration, and efficiency (Lin, Tsai, Fang, & Liu, 2011).

Narcolepsy

Narcolepsy is a disorder of impaired expression of wakefulness and REM sleep (Chakravorty & Rye, 2003). Narcolepsy is characterized by excessive daytime sleepiness (EDS), cataplexy (sudden losses of muscle tone during waking), and sleep paralysis (sleep onset and offset) (Chakravorty & Rye, 2003; Nishino, 2007). The most common cause of narcolepsy is hypocretin/orexin ligand deficiency in the brain and cerebrospinal fluid (Chabas, Taheri, Renier, & Mignot, 2003; Chakravorty & Rye, 2003; Karnani et al., 2011; Nishino, 2007; Nishino & Kanbayashi, 2005). Hypocretin acts to maintain muscle tone (Nishino & Kanbayashi, 2005). The literature suggests that an abnormality of the immune system may trigger the loss of hypocretin-producing neurons in people with narcolepsy (Chabas et al., 2003).

Food and Herb Suggestions for Narcolepsy

Herbs	Rationale
Gotu kola	• Gotu kola wort boosts energy levels and possesses antioxidant properties (Balch, 2006). • Gotu kola is used to reduce fatigue, anxiety, and depression and improve memory and intelligence (Garner-Wizard, Henson, Milot, Minigh, Oliff, & Oppel, 2007). • Stimulates conversion of glutamic acid to GABA (Head & Kelly, 2009).
	Explanations: • In some persons it can cause gastrointestinal upset and nausea (Garner-Wizard, Henson, Milot, Minigh, Oliff, & Oppel, 2007).
St John's wort	• St John's wort boosts energy levels and possesses antioxidant properties (Balch, 2006).
Ginkgo biloba	• Ginkgo biloba improves and promotes blood circulation to brain and is a powerful antioxidant for protecting brain cells (Balch, 2006).
	Explanations: • Ginkgo can increase bleeding risk in patients with bleeding disorders and those taking conventional antiplatelet or anticoagulant agents (Barnes, 2010). • Ginkgo may also cause headaches, seizures, irritability, hyphema, palpitations, dizziness, or rash in some individuals (Barnes, 2010).
Foods	**Rationale**
Eat a low-fat diet high in cleansing foods such as leafy green vegetables and sea vegetables. Also eat foods high in B vitamins, such as brewer's yeast and brown rice (Balch, 2006; Head & Kelly, 2009).	• Food high in fat and cholesterol can cause abnormal cortisol levels. • Vitamin B6 is a cofactor for several neurotransmitters such as serotonin and dopamine. • Vitamin B12 normalizes circadian rhythms. • Vitamin B3 increases rapid eye movement (REM) sleep and improves both quality and quantity of sleep by converting tryptophan to serotonin (Head & Kelly, 2009; Sarrafi-Zadeh et al., 2012).
Eat foods high in protein in the middle of the day. Eat foods complex in carbohydrates for the evening meal (Balch, 2006).	• High-protein foods increase alertness, whereas carbohydrates have a calming effect and can promote sleepiness (Balch, 2006). • High-protein foods include the amino acid tyrosine (Attele et al., 2000; Balch, 2006). • Tyrosine is a precursor for the neurotransmitter dopamine (Head & Kelly, 2009). • Hypocretin cells are stimulated by nutritionally relevant mixtures of amino acids (Karnani et al., 2011).

REM Sleep Behavior Disorder

Rapid eye movement sleep behavior disorder (RBD) is a parasomnia (Mahowald, Schenck, & Cramer Bornemann, 2007). It is also a common manifestation of narcolepsy (Iranzo, Santamaria, & Tolosa, 2009; Mahowald et al., 2007). Rapid eye movement sleep behavior disorder is classified as idiopathic (IRBD) or secondary according to causes (Iranzo et al., 2009). There is loss of the normal muscle atonia during REM sleep associated with disruptive motor activity related to the acting-out of dreams. This situation is strongly associated with neurodegenerative diseases such as multiple-system atrophy, Parkinson disease, dementia with Lewy bodies, spinocerebellar ataxias (Iranzo et al., 2009), and progressive supranuclear palsy (Gagnon, Postuma, Mazza, Doyon, & Montplaisir, 2006). The mechanisms underlying RBD may be related to complex multiple neurotransmitter dysfunction involving GABAergic, glutamatergic and monoaminergic systems. Rapid eye movement sleep behavior disorder is mediated by neither direct abnormal alpha-synuclein inclusions nor striatonigral dopaminergic deficiency alone (Iranzo et al., 2009).

Food and Herb Suggestions for Rapid Eye Movement (REM) Sleep Behavior Disorder

Herb	Rationale
California poppy	We can assume that California poppy is beneficial for REM sleep behavior disorder because: • The combination of poppy, passionflower, and valerian promotes sound sleep and beneficial REM sleep (Balch, 2006). • California poppy promotes calmness of the nervous system and relaxation (Balch, 2006).
	Explanations: Clonazepam has anxiolytic, anticonvulsant, muscle relaxant, and sedative effects. • Clonazepam is recommended for the treatment of REM sleep behavior disorder (Iranzo et al., 2009).
Valerian (*Valeriana officinalis*)	• We can assume that valerian is beneficial for REM sleep behavior disorder because: • Valerian inhibits enzyme-induced breakdown of GABA in the brain (Meoli et al., 2005).
Foods	**Rationale**
Eat foods such as dairy products, eggs, fish, and nuts (Balch, 2006).	• Dairy products, eggs, fish, and nuts all contain essential amino acids. • Melatonin is synthesized from the amino acid tryptophan. • Melatonin is effective in patients with REM sleep behavior disorder (Attele et al., 2000; Balch, 2006).
Eat foods such as tomatoes, rice, oranges, apples, bananas, cherries, cucumbers, cabbage, almonds, walnuts, and seeds (sunflower, mustard, and fennel) (Balch, 2006).	• These foods are high in melatonin (Balch, 2006).

Periodic Limb Movement in Sleep and Restless Legs Syndrome

Periodic limb movement (PLM) and restless leg syndrome (RLS) are common complex sleep disturbances (Alsaeedi & Ashammari, 2005). Periodic limb movement and RLS are parasomnias. They share the same pathophysiology and often respond to the same treatment (Natarajan, 2010). Periodic limb movement affects about 40% of people aged 65 years or older. As many as 80% of people with RLS also have PLMS. Periodic limb movement and RLS are characterized by typical periodic limb movement (Alsaeedi & Ashammari, 2005).

The symptoms of RLS have a diurnal pattern, and so the circadian temperature cycle has been suggested to have a role in the pathogenesis of RLS. Nigrostriatal presynaptic dopaminergic hypofunction, iron (Chaudhuri, Chaudhuri, Appiah-Kubi, & Trenkwalder, 2001), cobalamin and folate deficiency, structural abnormalities of the brainstem or cervical spinal cord hypofunction, high hypocretin-1 level, cerebellar and thalamic activation, and activation of the red nucleus and brain system have been suggested as causes of RLS and PLM (Chaudhuri et al., 2001).

Food and Herb Suggestions for Periodic Limb Movement (PLM) in Sleep and Restless Legs Syndrome (RLS)

Herbs	Rationale
Astragalus membranaceous	• *Astragalus membranaceous* improves functioning of all of the body's organ systems and boosts circulation (Liu, Song, Guo, Wang, & Zhou, 2013).
Aesculus hippocastum (horse chestnut)	• *Aesculus hippocastum* can relieve PLM and RLS by keeping blood flowing smoothly even during rest and sleep (Kalloo, Gamaldo, FAASM, Kwan, Salas, & Salas, 2014).
Ruscus aculeatus (butcher's broom)	• *Ruscus aculeatus* relieves pain and discomfort (Redman, 2000).
Chamomile	• Chamomile contains flavonoids and has a sedative effect. • It also binds BDZ and GABA receptors in the brain (Srivastava et al., 2010). • Chamomile is commonly used for muscle spasms (Srivastava et al., 2010).
	Explanations: • Chamomile causes allergic reactions (Srivastava et al., 2010).

Continued

Food and Herb Suggestions for Periodic Limb Movement (PLM) in Sleep and Restless Legs Syndrome (RLS)—cont'd

Food	Rationale
Eat foods such as dairy products, eggs, fish, and nuts.	• Tyrosine-rich foods can help increase dopamine levels. • High-protein foods include the amino acid tyrosine (Balch, 2006).
Eat foods high in B6 vitamins, such as leafy green vegetables, fish, poultry, and whole grains (Kitap). Eat foods rich in folate, such as leafy green vegetables and starchy beans, chickpeas and kidney and black beans (Balch, 2006).	• Vitamin B6 and folate are cofactors of dopamine and serotonin (Meoli et al., 2005).
Eat kiwi fruit	• Kiwi fruit is rich in folate (Lin et al., 2011). • There is a relation between folate deficiency and RLS (Chaudhuri, Chaudhuri, Appiah-Kubi, & Trenkwalder, 2001).

Sleep-Disordered Breathing

The most important cause of sleep disruption is sleep-disordered breathing (SDB), which includes sleep apnea syndrome and restrictive-parenchymal pulmonary diseases that present with nocturnal hypoventilation and hypoxemia (Canessa & Ferini-Strambi, 2011; Roepke & Ancoli-Israel, 2010).

Sleep-disordered breathing is associated with risk factors such as older age, gender, obesity, large neck, upper airway structural abnormalities, symptomatic status, endocrine abnormalities, sedating medications, alcohol consumption, family history, race, smoking, and upper airway configuration (Canessa & Ferini-Strambi, 2011; Roepke & Ancoli-Israel, 2010).

Cessation of breathing in SDB leads to repeated arousal from sleep as well as reductions in blood oxygen levels over the course of the night, resulting in nighttime hypoxemia (Matheson, 2008; Roepke & Ancoli-Israel, 2010). Sleep-disordered breathing is related to HPA hyperactivity. Sleep-disordered breathing displays HPA hyperactivity, disturbed sleep, and psychiatric and metabolic impairments (Buckley & Schatzberg, 2005).

Food and Herb Suggestions for Sleep-Disordered Breathing

Herb	Rationale
Chamomile	• Chamomile contains many terpenoids and flavonoids. • Chamomile preparations are commonly used for muscle spasms. • Apneic events usually result from complete or partial occlusion of the airway (Srivastava et al., 2010).
	Explanations: • Chamomile can increase the risk of bleeding. • Chamomile has significant antiplatelet activity (McKay & Blumberg, 2006).
Food	**Rationale**
Avoid high-calorie foods that cause weight gain.	• There is link between sleep disturbance and higher body mass index (Sarrafi-Zadeh et al., 2012). • A meal consumed close to bedtime is associated with sleep disturbance (Sarrafi-Zadeh et al., 2012).

Circadian Rhythm Sleep Disturbance

The human circadian system is normally synchronized with the solar day. Misalignment of the circadian clock with the environmental cycle may result in sleep disturbance (Zisapel, 2001). Delayed sleep phase disorder, advanced sleep phase disorder, and non-entrained types of circadian rhythm sleep disturbance (CRSD) result from disorganization of the circadian system (Hida, Kitamura, & Mishima, 2012). Among these are chronic insomnias associated with an endogenous clock that runs slower or faster than the norm (delayed or advanced sleep phase syndrome, or irregular sleep–wake cycle), periodic insomnia due to disturbances in light perception (non–24-h sleep–wake syndrome and sleep disturbance in blind individuals), and temporary insomnia

Food and Herb Suggestion for Circadian Rhythm Sleep Disturbance (REM)

Herb	Rationale
Valerian (*Valeriana officinalis*)	We can assume that valerian is beneficial for REM sleep behavior disorder because: • Valerian is a melatonin supplement (Balch, 2006).
	Explanations: • Melatonin is recommended for the treatment of REM sleep behavior disorder (Balch, 2006).
Foods	**Rationale**
Eat foods high in B vitamins, such as brewer's yeast and brown rice (Balch, 2006; Head & Kelly, 2009).	• Foods high in fat and cholesterol can cause abnormal cortisol levels. • Vitamin B6 is a cofactor for several neurotransmitters such as serotonin and dopamine. • Vitamin B12 normalizes circadian rhythms. • Vitamin B3 increases REM sleep and improves both quality and quantity of sleep by converting tryptophan to serotonin (Head & Kelly, 2009; Sarrafi-Zadeh et al., 2012).

owing to social circumstances (jet lag and shift-work sleep disorder) (Bjorvatn & Pallesen, 2009; Hida et al., 2012; Zisapel, 2001).

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Chapter 28

Fragmented Sleep and Memory Consolidation

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SLEEP ARCHITECTURE

Here we will focus on one specific aspect of sleep architecture, sleep continuity, and discuss the potential implications of its disruption. Sleep architecture describes sleep's components, stages, and cycles and their interrelationships. Two basic types of sleep are non–rapid eye movement (NREM) sleep and rapid eye movement (REM) (Dement & Kleitman, 1957). In humans, NREM sleep is divided into stages 1–4. Each stage has unique characteristics including variations in brain wave patterns, eye movements, and muscle tone. Throughout the night, NREM sleep and REM sleep constitute about 75–80% and 20–25%, respectively. These stages are not equally distributed, with the first part of the night dominated by NREM sleep and the second part containing more REM sleep. Sleep proceeds in cycles of REM and NREM, usually four to five of them per night. The average length of the first NREM–REM sleep cycle is 70–100 min. The second and later cycles are longer lasting, approximately 90–120 min (Kryger, Roth, & Dement, 2010). Stage 1 of NREM sleep is the transitional stage between wakefulness and sleep. Thus, in most people, a sleep episode begins in NREM stage 1, which usually lasts 1–7 min in the initial cycle, constituting 2–5% of total sleep. Stage 1 is characterized by a low sensory awakening threshold, and therefore can be easily interrupted and fragmented. Brain activity on the electroencephalogram (EEG) in stage 1 transitions from wakefulness (marked by rhythmic alpha waves) to low-voltage, mixed-frequency waves. NREM sleep stage 2 lasts approximately 10–25 min in the initial cycle and lengthens with each successive cycle, eventually constituting between 45% and 55% of the total sleep episode. The sensory threshold for arousal in this NREM sleep stage is higher than in stage 1 and it is generally characterized by a less fragmented sleep pattern than stage 1. Brain activity on an EEG shows relatively low-voltage, mixed-frequency activity, characterized by the presence of sleep spindles and K-complexes. Sleep stages 3 and 4 are collectively referred to as slow-wave sleep (SWS), most of which occurs during the first third of the night (Kryger et al., 2010). Stage 3 lasts only a few minutes and constitutes about 3–8% of sleep. The EEG at stage 3 shows increased high-voltage, slow-wave activity. Sleep stage 4 makes up about 10–15% of sleep and is characterized by intensified high-voltage, slow-wave activity on the EEG. The sensory arousal threshold at this sleep stage is high and it is therefore mostly continuous.

Rapid eye movement sleep is defined by the presence of desynchronized (low-voltage, mixed-frequency) brain wave activity and bursts of rapid eye movements. During the initial cycle, the REM period may last only 1–5 min; however, it becomes progressively prolonged as the sleep episode progresses. A hallmark of REM sleep is generalized muscle atonia (Kryger et al., 2010; Sakai et al., 1979).

Sleep architecture is not fixed throughout life and changes continuously with age (Kryger et al., 2010). The speed at which sleep is initiated, its continuity, the percentage of time spent in each stage of sleep, and overall sleep efficiency change from infancy to adulthood (Kryger et al., 2010). Examination of sleep characteristics by age

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and the contribution of sleep to specific physiological functions at different ages may help elucidate the functional role of sleep.

DISORDERS OF SLEEP ARCHITECTURE

There are different types of sleep disorders, including abnormal sleep behavior, circadian rhythms sleep disorders, excessive daytime sleepiness disorders, insomnia, and other sleep abnormalities induced by other pathological conditions. For example, depression, Alzheimer disease, asthma, dementia, and epilepsy all can affect sleep (Kryger et al., 2010). These pathological conditions and some normal life circumstances affect various aspects of sleep architecture. For example, in narcolepsy, orchestrated transitions between sleep stages are impaired, and instead of entering sleep through NREM, individuals with narcolepsy enter sleep directly into REM sleep (Kryger et al., 2010). Insomnia is another sleep disorder characterized by difficulty falling and/or staying asleep. In these patients there is a significant impact on overall sleep duration (Sutton, 2014). Other disorders affect other aspects of sleep, including sleep continuity and the timing of sleep.

One aspect of sleep architecture that is often interrupted in various normal and clinical conditions is sleep continuity. Many people in modern society experience disruption of sleep due to work responsibilities, care-giving, or lifestyle choice. Continuity of sleep is specifically affected in sleep apnea, disordered breathing, normal aging, or pregnancy (Pien & Schwab, 2004; Kryger et al., 2010).

Obstructive sleep apnea syndrome (OSAS) is a common cause of sleep fragmentation. It is characterized by repetitive episodes of upper airway obstruction during sleep (Myers, Mrkobrada, & Simel, 2013). Patients with sleep apnea are subjected to recurrent and chronic sleep fragmentations along with intermittent hypoxia and hypercarbia. Nevertheless, the total sleep time in these patients is only slightly affected (Coleman et al., 1982). It is considered that approximately 13% of men and 6% of women among adults aged 30–70 years have moderate to severe sleep-disordered breathing (Kilpinen, Saunamäki, & Jehkonen, 2014). Sleep apnea is commonly associated with excessive daytime sleepiness, reduced quality of life, mood changes, and cognitive changes especially in attention, executive functioning, and memory (Kilpinen et al., 2014). Continuous positive airway pressure (CPAP) treatment is the most common form of treatment in moderate and severe OSAS. Continuous positive airway pressure provides constant pressure to offset airway collapse, thereby maintaining airway patency (Myers et al., 2013). With properly titrated pressure, it minimizes sleep-disordered breathing events (Myers et al., 2013). The prevalence of sleep apnea, which is characterized by sleep fragmentation, is an important motivation to study the role of sleep continuity. It is also an important source of information to understand the impact of these fragmentations on sleep-related functions.

Another condition that has major impact on sleep continuity is normal aging. Aging is characterized by a diminished quality of sleep with decreased sleep duration and increased time awake after sleep onset. Older individuals often face difficulty staying asleep at night and awake during the day. They awaken more frequently and tend to awaken less from REM sleep and more from NREM sleep than young adults. Sleep architecture also begins changing in middle age, leading to a dramatic decrease in the deepest stage of NREM sleep as aging progresses (Petit et al., 2004). Non–rapid eye movement sleep itself is characterized in older adults by reduced numbers of sleep spindles and K-complexes. Of note, REM sleep is minimally affected during aging (Harand et al., 2012; Kryger et al., 2010). A study that compared NREM and REM sleep in young (2–4 months) and aged (22–24 months) mice also revealed sleep alterations with aging. The authors found that aged mice are less able to sustain long episodes of wakefulness or NREM sleep, and a spectral analysis of EEG recordings revealed that aging slows theta peak frequency, a correlate of arousal (Wimmer et al., 2013). These findings provide a window into mechanisms underlying the destabilization of long periods of sleep and wake and reduced vigilance that develop with aging.

As mentioned before, sleep of aged adults is often characterized by frequent sleep fragmentation, suggested to indicate diminished homeostatic sleep pressure. Moreover, the prevalence of sleep apnea dramatically increases with age. It is estimated that 42% of individuals over the age of 65 experience sleep apnea (Ancoli-Israel et al., 1991).

STUDYING SLEEP CONTINUITY

Sleep deprivation and sleep fragmentation are commonly found in both normal individuals and in patients with sleep disorders. As mentioned earlier, most available data on sleep fragmentation come from analyzing sleep in patients with sleep apnea and other sleep disorders. Studies in healthy volunteers and animal models that undergo experimental sleep deprivation or sleep fragmentation allow us to elucidate which symptoms are associated with sleep deprivation versus sleep fragmentation. Among the measurements used to evaluate sleep architecture (e.g., total sleep time, time in each sleep stage, time of wake after sleep onset, sleep efficiency, and sleep stage shifts), some monitor sleep continuity (i.e., the number of awakenings from sleep and measuring the lengths of episodes of continuous sleep). Different analysis techniques can be applied to sleep recording data to provide unique information regarding details of sleep continuity (Norman et al., 2006).

Clinical studies have examined the relationship between sleep fragmentation and daytime function. Carskadon,

Brown, and Dement (1982) looked at many sleep-related variables but found that only measures of arousal and measures of sleep-related respiratory events significantly correlated with daytime sleepiness.

Analysis of the functional outcomes of sleep fragmentation induced by apnea-associated oxygen desaturation has a major limitation because it does not allow us to discriminate between the impact of sleep interruption and the relative contribution of oxygen desaturation. Some studies have attempted to differentiate the effects of sleep fragmentation from the effects of apnea-associated oxygen desaturation. For example, Colt, Haas, and Rich (1991) treated sleep apnea patients with CPAP to reduce sleep fragmentation and daytime sleepiness before experimentally adding periods of oxygen desaturation with CPAP, to document that daytime sleepiness is not caused by periods of oxygen reduction alone. Patients with upper airway resistance syndrome have minimal oxygen desaturation and apnea; yet, these patients show periodic increases in airway resistance followed by arousal (Bonnet & Arand, 2003) and they have daytime sleepiness. In addition, experimentally induced sleep fragmentation studies in healthy volunteers enabled us to differentiate sleep fragmentation effects from desaturation effects, which further supports the idea that sleep fragmentation per se is important for the functional outcomes of sleep.

Sleep fragmentation studies in healthy individuals have other limitations. For example, the increase in arousals as a result of the experimentally induced fragmentations is normally accompanied by a change in overall sleep architecture (e.g., an increase in stage 1 sleep along with a decrease in SWS and REM). Several sleep fragmentation studies have carefully controlled total sleep time to show that the effects of sleep fragmentation are not produced by partial sleep deprivation (Martin et al., 1997; Stepanski et al., 1987). Another limitation of sleep fragmentation studies in humans relates to our capacity to induce sleep fragmentation in healthy human subjects for continuous periods. This is especially relevant to decipher the impact of sleep fragmentation on sleep apnea patients, for example, who have chronic sleep fragmentations. Animal models of sleep fragmentation offer an opportunity to overcome these limitations and allow us to monitor and systematically analyze the functional outcomes of sleep fragmentation.

THE FUNCTIONS OF SLEEP

From the functional perspective, sleep is still a mystery. We do not know what the major function of sleep is, but it is now established that sleep affects, among other factors, memory consolidation, mood, attention, metabolism, hormonal regulation, and immune activity (discussed in Frank, 2006; Krueger, Obál, & Fang, 1999; Tononi & Cirelli, 2006; Vassalli & Dijk, 2009). Our knowledge is even more limited with respect to the relative contribution of sleep architecture on the functional outcomes of sleep.

Experimentally, only a limited number of studies have focused on this aspect of sleep (disrupted sleep continuity) and even fewer have directly compared the effects of sleep fragmentation and sleep deprivation on memory. Here, we will summarize the major reports on the effects of sleep fragmentation on cognitive functions and especially memory consolidation.

Sleep and Memory Consolidation

The role of sleep in the retention of memory was established in past decades. Early theories suggested a passive role for sleep in enhancing memories by protecting them from interfering stimuli. However, increasing data in recent years indicate that sleep has an active role in memory consolidation during sleep. Most findings support the role of NREM sleep in the memory consolidation process (recently reviewed in Rasch & Born, 2013). Some studies suggest that REM sleep may also affect specific aspects of memory consolidation (Ackermann & Rasch, 2014; Cairney et al., 2014). The standard two-stage memory model for declarative memory assumes that new memories are transiently encoded into temporary storage (represented by the hippocampus in the declarative memory system) before they are gradually transferred into long-term storage (mainly represented by the neocortex) or are forgotten. It was suggested that sleep is an optimized state for memory consolidation, allowing flow of information for long-term storage (Abel et al., 2013; Rasch & Born, 2013). It was further suggested that memories are also reorganized during sleep by integrating into existing schemes, dissection of the gist (Wagner et al., 2004), and inspiring insight (Abel et al., 2013; Rasch & Born, 2013; Stickgold & Walker, 2013).

Studies have shown that hippocampal place cells, activated during training, are reactivated in the same sequential order during subsequent periods of sleep (Wilson & McNaughton, 1994), which may contribute to memory consolidation. Some evidence indicates that a similar phenomenon exists in humans. It was shown that the hippocampus, activated during a spatial learning task, was reactivated during post-learning NREM (Peigneux et al., 2004) and the amount of hippocampal activity during SWS was positively correlated with overnight improvement of memory performance. It was also shown that reactivation can be experimentally induced by associative cues (Antony et al., 2012; Rasch et al., 2007). Brain oscillations during sleep also affect memory consolidation. Spindle density, spindle activity, and the frequency of hippocampal ripples are increased during post-learning sleep (Fogel et al., 2011; Girardeau & Zugaro, 2011; Harand et al., 2012). Moreover, inducing slow oscillation-like potential fields during post-learning sleep with transcranial direct current stimulation

increase time spent in NREM sleep, enhance EEG power in the slow oscillation frequency band and in the slow spindle band, and improve retention on an episodic memory task (Marshall et al., 2006).

FUNCTIONAL OUTCOMES OF SLEEP FRAGMENTATION

The past decade's researchers have focused on the effects of sleep fragmentation on neurobehavioral, cardiovascular, metabolic, immune, and other outcomes of fragmented sleep. We will discuss some of these studies, mostly in the context of memory consolidation.

Memory and Cognitive Outcomes of Sleep Fragmentation

Deprived sleep conditions particularly impair the ability to retain new information and disrupt memory consolidation (Abel et al., 2013; Karni et al., 1994; Polzella, 1975; Rasch & Born, 2013). Studies have shown that sleep fragmentation affects cognitive performance above and beyond those accounted by changes in sleep duration (Martin et al., 1996). Experimental sleep fragmentation in humans is associated with decreased cognitive processing speed, and impaired reaction time independent of effects attributable to changes in the quantities of sleep states. For example, one study tested for psychometric test results, mood, a multiple sleep latency test, and maintenance of wakefulness test after a night of experimentally induced sleep fragmentations. They used sound pulses every 2 min to fragment sleep. The sound volume and duration were titrated to result in a return to theta or alpha rhythm on the EEG for at least 3 s. The researchers found that one night of sleep fragmentation increases daytime sleepiness, impairs subjective assessment of mood, and decreases mental flexibility and sustained attention (Martin et al., 1996). Other evidence suggests that uninterrupted sleep for a minimum length of time is required for optimal daytime vigilance and neurocognitive function (Bonnet, 1987; Bonnet, 1989; Downey & Bonnet, 1987; Roehrs et al., 1994; Stepanski, 2002; Stepanski et al., 1987).

Some studies attempted to dissect in sleep apnea patients the relative contribution of sleep fragmentation on the effects on memory and cognitive functions. One study evaluated episodic memory, with an emphasis on the recollection of spatial and temporal contexts, in patients with OSAS and healthy controls. They found that although attention was only slightly disturbed, recollection was strongly disturbed in patients and the number of micro-arousals was the best predictor of memory deficit (Daurat et al., 2008). Another study compared performance on a motor sequence learning task in relatively young subjects with obstructive sleep apnea. They found a significant difference in the primary outcome of immediate overnight improvement on the motor sequence learning task between groups. Here again, this difference was predicted by the arousal index rather than oxygen saturation (Djonlagic et al., 2012).

Interestingly, it was also suggested that specific fragmentation of REM sleep might lead to dysfunction in the emotional neural network, including limbic and paralimbic areas that are specifically activated during REM sleep (Riemann et al., 2012).

A study that challenges the contribution of sleep fragmentation to memory consolidation focused on pregnant women (Berndt et al., 2014). Pregnant women, both before and after childbirth, frequently experience memory deficits and disrupted sleep. This study assessed the relationship between false memory generation and fragmented sleep during pregnancy and motherhood, and revealed that compared with controls, the group of pregnant women produced more false memories and displayed more fragmented sleep both during pregnancy and after childbirth. However, false memory generation was not correlated to measures of sleep fragmentation, which leaves open the question regarding whether both phenomena are related.

Conditions of fragmented sleep such as apnea, aging, or pregnancy are accompanied by other physiological changes that can mask the specific contribution of sleep fragmentation to memory consolidation. One example is cholinergic neurotransmission, which, if impaired, can affect memory formation and increases sleep fragmentation (Queiroz et al., 2013). Moreover, it is possible that acute sleep fragmentation (i.e., an experimental paradigm in normal subjects) and chronic disruption of sleep continuity (e.g., aging, sleep apnea), will have different effects on memory consolidation.

In rodents, experimental sleep fragmentation is associated with deficits in attentional set-shifting (McCoy et al., 2007) and visuospatial learning (Tartar et al., 2006). In these studies only modest changes in the quantities of sleep stages were identified. Rodent studies using short-term sleep fragmentation paradigms also confirmed the adverse effects of this sleep manipulation on learning. Induced sleep fragmentation in rats using a custom treadmill, designed to induce locomotor activity every 2 min throughout a 24-h period, revealed that sleep fragmentation before testing in a Morris Water Maze impairs the ability to retain spatial reference memories (Ward, McCarley, & Strecker, 2009) and sleep fragmentation after acquisition impairs memory consolidation and retention (Ward, McCoy, et al., 2009). It was also shown in the same experimental model that sleep fragmentation reduces hippocampal CA1 pyramidal cell excitability and response to adenosine (Tartar et al., 2006).

One theory is that sleep induces repair, restoration, and detoxification by removing oxidants produced during waking time (Benington & Heller, 1995; Honda, Komoda, & Inoué, 1994), thereby decreasing oxidative stress (Kumar & Kalonia, 2007). Some therefore argue that sleep disruption elicits oxidative stress and cellular damage. The

overall result is an imbalance between the generation of reactive oxygen species (ROS) and clearance by endogenous antioxidant defense systems in discrete areas of the brain (D'Almeida et al., 1997; Everson, Laatsch, & Hogg, 2005; Singh et al., 2008; Süer et al., 2011). Sleep deprivation has been reported to cause oxidative stress, resulting in the formation of ROS eventually leading to neuronal and cellular damage (Gopalakrishnan, Ji, & Cirelli, 2004). Nicotinamide adenine dinucleotide phosphate (NADPH) oxidase is a major source of ROS generation in most mammalian cells including neurons, either as a byproduct of their normal catalytic activity or as a result of aberrant functioning in disease (Bedard, Lardy, & Krause, 2007). The ROS generated by NADPH oxidases has critical roles in various physiological processes, including innate immunity, modulation of redox-dependent signaling cascades, and as cofactors in the production of hormones. Sleep deprivation affects oxidative stress in the brain (D'Almeida et al., 1997; Everson et al., 2005; Singh et al., 2008; Süer et al., 2011) and a specific effect was shown on hippocampal oxidative stress induced by sleep deprivation in mice (Silva et al., 2004). In addition, it was recently shown that sleep has a critical function in ensuring metabolic homeostasis (Xie et al., 2013). It is unclear, however, whether these factors are differentially affected by sleep deprivation and sleep fragmentation.

The specific contribution of sleep fragmentations to these effects is largely unknown. Recently, it was shown that the oxidative stress responses and neurobehavioral impairments induced by intermittent hypoxia during sleep were partially mediated by excessive NADPH oxidase activity (Nair, Zhang, et al., 2011). In another study from the same group (Nair, Dayyat, et al., 2011), the authors demonstrated that 12 h sleep fragmentation for 14 days, which aimed to mimic sleep apnea, interfered with spatial learning and retention memory tests in a well-defined hippocampal-dependent learning and memory task.

These studies add an essential mechanistic understanding of the role of continuous sleep in memory consolidation. However, some of these studies were limited by the method of sleep fragmentation. For example, sensory stimulation (tone) used to induce arousal may actively interrupt neuronal processes, and the sleep fragmentation paradigm that uses physical activity to fragment sleep may induce some levels of stress, which in turn, can also impair memory. Despite these limitations, to various extents these paradigms mimic the physiological events of fragmented sleep. For instance, many sleep fragmentation conditions in normal patients are induced by environmental cues and often include increased motility.

We attempted to overcome these technical limitations by developing an optogenetic model of sleep fragmentation in mice (Rolls et al., 2011). We expressed the light-sensitive Channelrhodopsin-2 (ChR2) cation channel in hypocretin/orexin neurons in the lateral hypothalamus. This enabled us to control the activity of these neurons known to induce arousal. We then adjusted the stimulation pattern of these neurons to induce sleep fragmentation at different intervals, resulting in micro-arousals (<2 s). Experiments consisted of training mice in a novel object task, with testing occurring 24 h later. For 4 h immediately after the novel object task training session, the mice were undisturbed, were totally sleep deprived by gentle handling, or had their sleep fragmented by optogenetic stimulation in 30-, 60-, 120-, or 240-s intervals. The mice were allowed to sleep ad lib for the remaining 20 h before testing. Analysis of the mice's performance in the novel object test was normal in control mice that were allowed to sleep. Performance differed in the groups receiving optogenetic stimulation of the hypocretin neurons. Mice whose sleep was fragmented at 30- or 60-s intervals showed no long-term memory of the novel object. However, mice whose sleep was fragmented at 120- or 240-s intervals showed normal long-term memory of the novel object recognition (NOR) training (Figure 1). Our conclusion is that a minimal quantum of continuous NREM sleep is essential for memory consolidation.

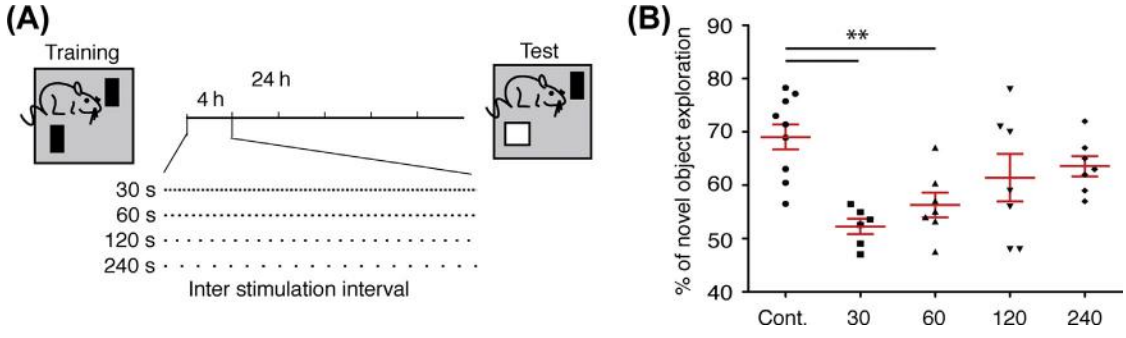

FIGURE 1 Effect of optogenetic sleep fragmentation on novel object recognition memory. (A) Schematic representation of the behavioral paradigm. Hcrt stimulations were introduced in four different intervals (schematic view). (B) Percentage of novel object exploration (out of the total time) for each mouse is shown (n = six to nine per group). The red lines represent Means ± SEM; One-way ANOVA (**$p < 0.01$).

As mentioned before, aging is characterized by changes in sleep architecture–increased fragmentation of sleep and rest–activity patterns (Carskadon et al., 1982; Harand et al., 2012; Petit et al., 2004; Singh et al., 2008; Wimmer et al., 2013). Normal aging is also characterized by declines in working memory and new episodic memory performance with relative sparing of semantic memory, recognition memory, and priming. Memory systems impacted by aging are associated with volumetric and functional changes in fronto-striatal circuits along with more limited changes in medial temporal structures. Cross-sectional studies generally associate poorer sleep quality with poorer neuropsychological functioning (Harand et al., 2012). It was suggested that the increase in sleep fragmentation accounts for reduced sleep-dependent memory consolidation with normal aging (Pace-Schott & Spencer, 2014). One study has shown that increased fragmentation of rest–activity patterns are associated with decreased cognitive function in older individuals (Lim et al., 2012). Nevertheless, older adults appear to be more resistant to the cognitive effects of sleep deprivation, restriction, and fragmentation than younger adults (Münch et al., 2004; Pace-Schott & Spencer, 2014).

SUMMARY

In modern society, sleep fragmentation is a common condition. The functional outcomes of this form of sleep disruption are still unclear. However, it is evident that sleep continuity is crucial for sleep-dependent memory consolidation. During aging, the dependency of memory consolidation on sleep is less profound, and thus older adults may be less affected by sleep disorders that accompany normal aging. Further studies will allow us to systematically compare and analyze the relative contribution of specific features of sleep architecture on sleep functions.

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Chapter 29

Sleepiness at the Wheel and Countermeasures: Effects of Caffeine, Napping, and Blue Light

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INTRODUCTION

Vehicular accidents may occur when a driver becomes drowsy or falls asleep, which results in decreased braking and steering capabilities. Furthermore, sleepiness-related accidents often occur at high speeds, leading to a greater mortality rate or risk of serious injuries (Horne & Reyner, 1995). One study conducted with 19,000 participants across five European countries found that excessive daytime sleepiness (EDS) occurred in as many as 15% of participants (Ohayon, Priest, Zulley, Smirne, & Paiva, 2002). The main causes of EDS are (1) lack of sleep, (2) disruption of circadian rhythms, (3) deterioration in the quality of sleep owing to sleep-disruptive events, and (4) primary hypersomnia.

Insufficient sleep has become a multinational problem. In a study conducted on the general population in Finland, 20.4% of participants were found to have insufficient sleep (Hublin, Kaprio, Parinen, & Koskenvuo, 2001), whereas a study conducted in Japan revealed that 28% of individuals had less than 6 h of sleep each night (Ohida et al., 2001). People with chronic sleep deprivation often have EDS. However, although an accumulated lack of nocturnal sleep can result in serious deficits in neurobehavioral function, it results in a mild increase in subjective sleepiness. That is, people with chronic lack of sleep may underestimate their own sleepiness (Van Dongen, Maislin, Mullington, & Dinges, 2003).

In this chapter, we review a number of studies examining the relationship between lack of sleep and the incidence of traffic accidents. We also discuss recent studies on the effectiveness of countermeasures for sleepiness among drivers.

LACK OF SLEEP AND ACCIDENTS

In a previous study, we analyzed traffic accidents that occurred in an area of Japan for 10 years, excluding those caused by drunk driving, to identify the correlation between traffic accidents due to falling asleep at the wheel and sleep duration on the day before the accident (Abe, Komada, Nishida, Hayashida, & Inoue, 2010). Our analysis of the time of day when each accident occurred revealed that rear-end collisions occurred most frequently between 8:00 and 9:00 am, whereas single-car accidents occurred more frequently during the night than during the day; thus, the type of accident differs by the time of the accident (Figure 1). The risk of rear-end collisions grows with increased traffic density, especially during the morning rush hour, which may lead to less space between cars. In contrast, the occurrence of single-car accidents may be attributed to low nighttime traffic density, leading to reduced driver alertness and increased speed. For both rear-end collisions and single-car accidents, a higher percentage of drivers had less than 6 h of sleep on the day before the accident than for other types of accidents. Multivariate

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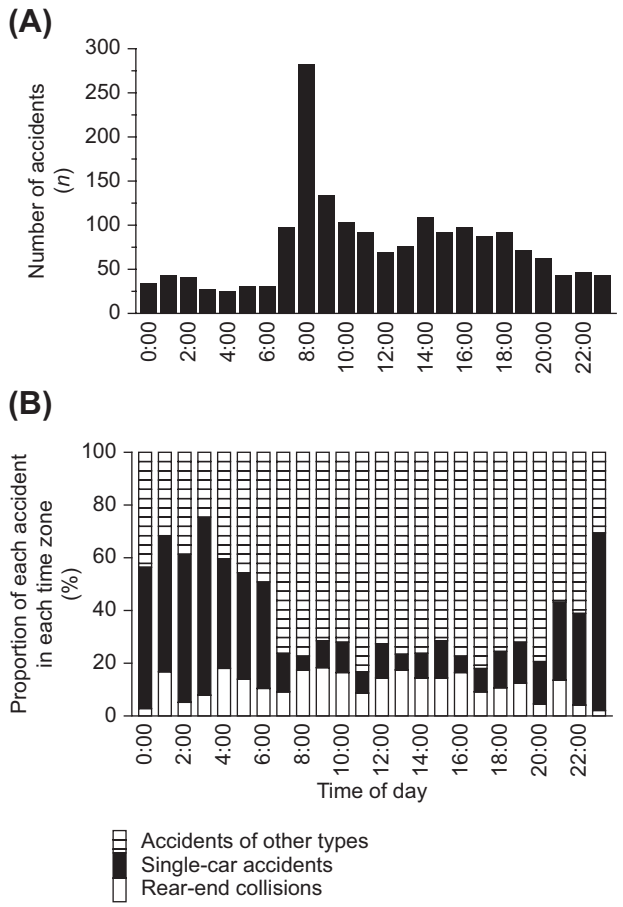

FIGURE 1 (A) Time of day distribution of all accidents, (B) proportion of rear-end collisions, single-car accidents, and other accidents in each time zone (Abe et al., 2010).

logistic regression analysis showed that the occurrence of rear-end collisions was significantly associated with sleep duration of less than 6 h and more frequent driving, whereas the occurrence of single-car accidents was significantly associated with younger age and sleep duration of less than 6 h.

In another study, we administered a questionnaire to approximately 4000 nonprofessional drivers and investigated factors associated with self-reported motor vehicle accidents (MVAs). Self-reported sleep duration on weekdays of less than 6 h, more than 6 h, and less than 7 h, and loud snoring or apnea reported by family members were all associated with an increased risk of MVAs (Abe, Komada, Asaoka, Ozaki, & Inoue, 2011). This result suggests that to prevent sleep-related MVAs, drivers should have adequate nocturnal sleep and undergo screening for obstructive sleep apnea syndrome (OSAS), which may cause frequent sleep fragmentation, possibly leading to elevated sleepiness.

SHIFT WORK AND ACCIDENTS

Circadian rhythm length in humans (i.e., the sleep–wake cycle, secretion rhythm of melatonin, and core body temperature) exceeds 24 h under constant dark conditions without time information, because light–dark changes and time cues are crucial for maintaining a constant circadian rhythm. Normally, the circadian rhythms of the sleep–wake cycle, core body temperature, and melatonin secretion run synchronously. Core body temperature becomes lowest in the middle of nocturnal sleep and highest in the afternoon. In addition, secretion of melatonin starts a few hours before sleep onset, promoting human sleep. However, when a forced change in the sleep–awake pattern (desynchronization) occurs, EDS can occur. The most common cause of desynchronized circadian rhythms in modern society is rotating shift work. The rate of persons engaged in shift work (i.e., permanent night, rotating, and evening shifts) is difficult to determine because estimates vary depending on the definition used and the region studied. In the United States, 17.7–25.9% of the total workforce starts work between 14:00 and 18:30 (McMenamin, 2007). These data suggest that between 25.8 and 37.8 million U.S. adults are engaged in shift work on a regular or rotating basis. Data from other countries also indicate that a high proportion of the populations are engaged in shift work: 22% in the United Kingdom, 13% in Australia, 25% in Greece, 25% in Finland, and 19% in Japan (Boisard, Cartron, Gollac, & Valeyre, 2003; Drake & Wright Jr., 2011; Japan Ministry of Health, Labor and Welfare, 2007).

Shift-work disorder (SWD) is a sleep disorder related to shift work that causes EDS and/or problems with nocturnal sleep (American Academy of Sleep Medicine, 2005). Shift-work disorder occurs because shift workers must stay awake and sleep at different times than that determined by their internal clock. As a result, they are likely to have insufficient sleep (Åkerstedt, 2003). In a study by Scott et al. (2007), 600 of 895 nurses reported that they had fallen asleep at the wheel at least once. The prevalence of SWD has been reported as 32.1% in night workers (Di Milia, Waage, Pallesen, & Bjorvatn, 2013), 28.9% in nurses on a two-shift rotation (Flo et al., 2012), 44.3% in those on a three-shift rotation (Flo et al., 2012), and 24.4% in those on rapid-rotation schedules in Japan (Asaoka et al., 2013). Our previous study on 3109 participants engaged in shift work as public transportation drivers found that SWD was the main predictor of EDS (Asaoka, Namba, Tsuiki, Komada, & Inoue, 2010). Notably, the severity of subjective sleepiness in drivers with SWD was higher than that of drivers with OSAS, which is widely accepted as the major cause of EDS (Asaoka, Namba, Tsuiki, Komada, & Inoue, 2010). Workers who meet the criteria for SWD are likely to have accidents related to sleepiness (Drake, Roehrs, Richardson, Walsh, & Roth, 2004). However, SWD is often undiagnosed and untreated (Schwartz & Roth, 2006). It is important to perform systematic SWD screening to maintain both the physical and mental health of workers and to ensure traffic safety, because shift workers are no longer a small minority and approximately

50% of professional drivers have irregular schedules or are engaged in night driving (Pack et al., 2002).

There are several coping strategies for SWD, such as taking a short nap before or during night shifts, using bright light exposure and melatonin at appropriate times, and using drugs such as modafinil as needed to stay awake (Schwartz & Roth, 2006).

COUNTERMEASURES

As mentioned previously, EDS is a common phenomenon frequently observed in the general population and has a negative impact on everyday life (Ohayon, Caulet, Philip, Guilleminault, & Priest, 1997). Up to 20% of all traffic accidents in industrial societies are sleep-related (Connor et al., 2002; Horne & Reyner, 1995). Connor et al. (2002) showed that driving between 2:00 and 5:00 am multiplies the risk of traffic accidents by 5.6. Despite this, many professional drivers repeat this dangerous behavior because of financial (Arnold et al., 1997) or sociocultural reasons (Philip, Taillard, Quera-Salva, Bioulac, & Åkerstedt, 1999). Under this situation, traffic accidents at work or from the workplace to home are major causes of injury and death among workers (Personick & Mushinski, 1997).

There is enough evidence that sleepiness owing to shift work is associated with increased fatigue or sleepiness and constitutes a clear safety risk in some occupations. Although there are several studies on how to optimize work schedules (Knauth, 1997), including short rests between shifts and avoiding many night shifts, the issue of countermeasures for night work sleepiness continues to attract attention. Taking a nap just before or during night shift work is an important candidate for reducing night work sleepiness (Horne & Reyner, 1996; Sagaspe et al. 2007); however, convincing evidence of the effectiveness of napping or other countermeasures has not accumulated.

Allowing cold air into the car or listening to the radio have not demonstrated significant efficacy as countermeasures to sleepiness at the wheel; however, a number of studies have shown that taking a nap and drinking coffee are effective countermeasures (Horne & Reyner, 1996; Sagaspe et al. 2007). Nevertheless, these countermeasures have some limitations: individual differences in efficiency, limited duration of effect, and side effects (Taillard et al., 2012). In addition, many sleepy drivers (46%) do not use these countermeasures adequately (Anund, Kecklund, Peters, & Åkerstedt, 2008). Therefore, we explored differences in the use of effective countermeasures for sleepiness at the wheel (Asaoka, Abe, Komada, & Inoue, 2012). In that study, about 20% of both professional and nonprofessional drivers reported using napping to reduce sleepiness at the wheel; this was lower than countermeasures such as stopping to rest, drinking coffee, chewing gum, or opening windows. This finding is notably consistent with the results of Anund et al. (2008), which showed that napping was not the first choice among drivers to reduce sleepiness at the wheel.

Recently, blue light has been shown to be effective in reducing sleepiness and enhancing cognitive performance, and is supported by a study using tasks requiring concentration and cognition (Chellappa et al., 2011). Intrinsically photosensitive retinal ganglion cells that contain the photopigment melanopsin are known to respond directly to light with a peak spectral sensitivity in the short-wavelength range (460–480 nm blue light) (Berson, Dunn, & Takao, 2002) and progress to the suprachiasmatic nucleus (master biological clock) and to the brain area involved in the regulation of arousal (Gooley, Lu, Fischer, & Saper, 2003) using a specific nonvisual tract. Exposure to blue light for a certain time is effective for maintaining subjective and objective correlates of alertness and performance in the evening (Chellappa et al., 2011) and at night (Cajochen et al., 2005).

In the following sections, we review the effects on alertness of caffeine, napping, and blue light as countermeasures for sleepiness.

Caffeine

Caffeine is a widely used substance mainly consumed in coffee and other beverages. Adults in Western society are estimated to have an average all-source daily caffeine intake of about 200–300 mg per day (D'Amicis & Viani, 1993) and these amounts increase with age (Sanchez-Ortuno et al., 2005). Caffeine increases alertness and acutely reduces sleep propensity.

A previous experimental study showed that oral administration of a 240-mg dose of caffeine in the evening rapidly reduced subjective sleepiness and enhanced accuracy in a visual reaction test requiring a decision (Beaven & Ekström, 2013). Sagaspe et al. (2007) showed that drinking a cup of coffee containing 200 mg caffeine significantly improved nighttime highway driving performance in both young and middle-aged adults.

Preference for drinking coffee to counteract sleepiness at the wheel was associated with long annual driving distances and shorter periods after the acquisition of driving licenses for professional drivers. However, no other sleepiness-related variable such as the existence of diagnosed sleep disorders and snoring appeared to affect preference for drinking coffee (Asaoka, Abe, Komada, & Inoue, 2012). In contrast to nonprofessional drivers, professional drivers do not drink coffee in situations where sleepiness could be greater.

Several reports have demonstrated unfavorable effects of caffeine on sleep latency and quality (Sicard et al., 1996) and anxiety (Peeling & Dawson, 2007). Caffeine administration (2 mg/kg) has also been known to be associated with impaired recall in men presented with a word list, whereas the same facilitated recall in women (Arnold, Petros, Beckwith, Coons, & Gorman, 1987). Some of the effects of

caffeine have been attributed to expectancy (Elliman, Ash, & Green, 2010), although caffeine has psychoactive effects (Smith, Brice, Nash, Rich, & Nutt, 2003). Even the results of a double-blind study raised the possibility that some participants were conscious of the physiological stimulatory actions of caffeine and adjusted their subsequent behaviors accordingly (Beaven & Ekström, 2013). In addition, it has been suggested that individual differences in sensitivity may result from differences in absorption, distribution, or metabolism of caffeine, rather than differences in responsiveness to caffeine at sites of action in the brain (Goldstein, Warner, & Kaizer, 1965).

Napping

There is little evidence about workplace napping. A 1-year study of industrial plant workers who were allowed to have a 1-h nap on the night shift noted that napping was feasible and accepted, and improved workers' satisfaction with night work. The same study also noted higher self-reported vigilance after the nap and a resultant general improvement in quality of life (Bonnefond et al., 2001). In a study on aircraft engineers, a 20-min nap improved response times on a vigilance task at the end of a 12-h night shift compared with no nap, but only on the first 2 nights of consecutive shifts (Purnell, Feyer, & Herbison, 2002).

A nap is commonly used as a countermeasure for sleepiness at the wheel among middle-aged drivers who experienced a sleep-related traffic accident (Anund et al., 2008). It has also been reported in Europe that professional drivers (Anund et al., 2008), especially long-haul truck drivers (Hakkanen & Summala, 2000), are likely to take a nap as a countermeasure for sleepiness. In contrast, professional drivers in Japan are less likely to nap when they feel sleepy at the wheel than are nonprofessional drivers (Asaoka, Abe, Komada, & Inoue, 2012). Preference for napping was associated only with being male and previous experience of a traffic accident resulting from drowsy driving, which suggests that professional drivers do not take a nap until they have experienced a sleep-related vehicular accident (Asaoka, Abe, Komada, & Inoue, 2012). This may be because driving situations for Japanese professional drivers (e.g., pressure to meet deadlines) make it difficult for them to nap during work.

Napping preceding night work has been demonstrated as an effective countermeasure in both laboratory and field studies (Dinges, Orne, Whitehouse, & Orne, 1987; Schweitzer, Randazzo, Stone, Erman, & Walsh, 2006). Laboratory studies showed improvement on some performance measures after 1-h naps at night (Rogers, Spencer, Stone, & Nicholson, 1989). A 40-min scheduled nap during night shifts has also been reported to improve the mean and slowest 10% psychomotor vigilance task reaction time compared with no nap (Signal, Gander, Anderson, & Brash, 2009). However, this improvement did not seem sufficient to fully overcome the expected performance decline by the end of the night shift, and napping did not reduce the occurrence of lapses in performance during the shift (Signal et al., 2009). In addition, it was reported that one individual who had napped subsequently fell asleep when back on duty (Signal et al., 2009). This suggests that a nap affords some protective effect against performance deterioration but it is not a failsafe countermeasure to eliminate sleepiness during a night shift.

It was reported that a 30-min nap is more efficient for younger drivers than for middle-aged ones. That is, the performance of younger drivers was more improved than that of middle-aged drivers in the nap condition (Sagaspe et al., 2007). Sleep pressure is known to decrease with age (Mednick, Nakayama, & Stickgold, 2003). This might be explained by a lower homeostatic drive in middle-aged participants; middle-aged individuals have been reported to sleep less during napping than do younger individuals (Sagaspe et al., 2007). This could also explain why brief nocturnal sleep is not as restorative in this age group. Young people are also likely to have deeper sleep during naps, which is another explanation for the restorative power of naps. Buysse, Monk, Carrier, and Begley (2005) showed that older adults have a smaller and lower level of circadian variation in sleep propensity, compared with younger adults. However, psychomotor performance tends to show increased circadian variation among the elderly, which suggests that preventing deteriorated performance when sleepy may become increasingly difficult with age.

In conclusion, many previous experimental and intervention studies found that napping is effective in reducing drivers' sleepiness and improving driving performance (Asaoka, Abe, Komada, & Inoue, 2012; Horne & Reyner, 1996; Sagaspe et al., 2007). However, we should be careful regarding sleep inertia that may appear after taking a nap. Drivers, especially professional drivers and their employers (e.g., transportation companies), should know the benefits and drawbacks of napping when using this as a countermeasure for sleepiness at the wheel.

Blue Light

Light exposure has numerous effects on human physiology and behavior, such as better cognitive performance and mood. In particular, morning light exposure enhances cognitive performance, well-being, and mood even under mild sleep restriction (Gabel et al., 2013).

Recent studies have demonstrated that the alerting action of blue light is effective in reducing sleepiness and improving performance on tasks requiring concentration and cognition (Cajochen et al., 2011; Chellappa et al., 2011). The ability of short-light wavelengths to modulate alertness via the suppression of melatonin is well established (Cajochen et al., 2005; Wood, Rea, Plitnick, & Figueriro, 2013)

with greater suppression noted in light-eyed Caucasians (Higuchi, Motohashi, Ishibashi, & Maeda, 2007). Beaven and Ekström (2013) compared the physiological responses to blue light and caffeine, administered both separately and simultaneously. The authors hypothesized that similarities in the effect would be observed under the conditions of 240 mg caffeine and exposure to a 1-h dose of ~40 lx blue light on measures of cognitive function, reaction time, and wakefulness. The caffeine-only and blue light–only conditions enhanced the accuracy of participants in a visual reaction test requiring a decision, and an additive effect was observed with respect to the fastest reaction times. However, in a test for executive function, which included a task requiring distraction, caffeine exerted a negative effect on accuracy. Furthermore, blue light–only condition participants consistently outperformed caffeine participants when both congruent and incongruent distractions were presented. The blue light–only condition also had enhanced visual reactions in the absence of a decision or distraction; this effect was most prominent in blue-eyed participants. Overall, blue light and caffeine had distinct effects on psychomotor function and both have the potential to positively influence a range of activities in which cognitive function and alertness are important, such as in competitive sporting environments where, despite the widespread use of caffeine, the possible impact of blue light has received no research attention. Interestingly, the effects of blue light treatment on visual reaction time were mediated in part by the eye color of participants. Higuchi et al. (2007) speculated that the previously observed influence of eye pigmentation on wavelength-specific melatonin suppression could be extended to psychomotor effects independent of ethnicity (Beaven & Ekström, 2013).

A randomized controlled study showed that continuous blue light exposure during nocturnal driving resulted in a significant reduction of inappropriate line crossings and weaving compared with a placebo, and driving ability was improved to a level similar to the result of taking caffeine (Taillard et al., 2012). Both countermeasures resulted in driving closer to the center of the road. Continuous nocturnal blue light exposure is effective for short and long periods of driving, even at the circadian trough. The effect on alertness of blue light exposure was observed in both young and middle-aged drivers, even if light transmission, particularly for blue light, shows age-related effect reductions (Turner & Mainster, 2008). However, a recent report showed that the effect of blue light on brain response was diminished with aging in areas typically involved in visual functions and in key regions for alertness regulation and higher executive processes (Daneault et al., 2014).

Taillard et al. (2012) reported that although occasional exposure to continuous nocturnal blue light had no residual effect on the quantity and timing of subsequent sleep, 17% of drivers experienced eye-related discomfort and/or visual problems. This discomfort could impair the ability to maintain a stable lane position. The authors suggested that drivers should be informed about this side-effect and screening should be performed to identify blue light–intolerant drivers, who should not use blue light as a countermeasure for sleepiness at the wheel.

CONCLUSION

Sleep-related accidents are seen with increasing frequency in industrial societies. Although sleepiness at the wheel is a well-known risk factor for traffic accidents, many people drive at night, when alertness is at its lowest level. To date, caffeine and naps have been shown to be effective for sleepiness at the wheel. Light exposure, especially blue light, has recently been recognized as a potent means to stimulate alertness and cognition. Drivers should select countermeasures according to their age or individual physiology. Comparing professional and nonprofessional drivers, nonprofessional drivers are more likely to take countermeasures when they feel sleepiness or have the potential to experience sleepiness at the wheel. In recognition of this difference, transportation companies should adjust working schedules to allow for the use of countermeasures for drivers' safety.

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Chapter 30

Sleep Deprivation and Behavioral Risk-Taking

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What is wrong with losing a bit of sleep? Most people cut back on sleep now and then, and they generally seem to get away with it without much consequence other than feeling somewhat sluggish, inefficient, and cranky for a time—at least so they think. Emerging evidence suggests that sleep loss, both chronic and acute, is actually taking more of a toll on physical health and cognitive functioning than previously realized. Numerous studies have now linked sleep loss with poor physical health (Gangwisch et al., 2010; Luyster, Strollo, Zee, & Walsh, 2012; Sabanayagam & Shankar, 2010), reduced immune functioning (Wilder-Smith, Mustafa, Earnest, Gen, & Macary, 2013), altered insulin signaling and hormonal responses (Broussard, Ehrmann, Van Cauter, Tasali, & Brady, 2012), and even weight gain (Xiao, Arem, Moore, Hollenbeck, & Matthews, 2013). Likewise, it is well established that cutting back on sleep generally leads to temporary inattention, forgetfulness, slowing of response times, and decreased motivation (Durmer & Dinges, 2005; Killgore, 2010). On the other hand, compared to the large amount of research on the effects of sleep loss on physical health and elementary aspects of cognition, there have been relatively few studies examining the effects of insufficient sleep on other critical aspects of social and emotional functioning, such as risky decision-making and the willingness to take potentially dangerous chances (Killgore & Weber, 2014). A major concern for many occupations where decisions may have life-and-death consequences, such as medicine, transportation, public safety, and the military, is how insufficient sleep might affect the process of evaluating risk and the propensity to take action under conditions of varying uncertainty. This chapter provides a brief and selective overview of the small but emerging literature that has focused on how sleep loss can influence risk-taking behavior.

When considering the effects of sleep deprivation on cognition, it is critical to keep in mind that sleep is an exceptionally complex phenomenon; a comprehensive understanding of its functional significance still remains lacking. Because sleep serves multiple functions for the brain and body, its curtailment can affect multiple hierarchical brain systems, leading to any number of complex effects on behavior. Consequently, risk-taking behavior during periods of sleep loss may be the end product of alterations in many different cognitive systems individually or in tandem, potentially ranging from elementary deficits in simple attention to important details in the environment, to more complex changes in the valuation of rewards or their probabilities, or even to impairments in higher-order executive functions and social cognition. Here, we review several potential cognitive mechanisms whereby sleep loss might contribute to risky behavior.

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SIMPLE INATTENTION

At a basic level, good decisions are based on good information. Because humans base their decisions on information acquired through sensory input from the environment, anything that degrades the ability to reliably perceive and attend to incoming information will increase the risk associated with decisions where such information plays a crucial role. One of the most robust effects of sleep loss is a fundamental impairment of simple attention (Lim & Dinges, 2008, 2010). As the period of continuous wakefulness extends beyond about 16–18 h, individuals become prone to slowing of response times and brief lapses of sustained attention (Goel, Rao, Durmer, & Dinges, 2009). At times, the pressure to fall asleep can be so overwhelming that, despite intense efforts to remain awake, an individual will succumb to momentary periods involving a complete loss of consciousness referred to as "microsleeps" or frank "sleep attacks," depending on their duration (Durmer & Dinges, 2005). Even an attentional lapse of only a few seconds can mean that significant critical information may escape awareness. For instance, a sleepy driver who experiences a brief lapse while approaching a traffic light may make a risky choice to press down on the accelerator upon recognizing a yellow light, without realizing that the light had actually changed from green several seconds earlier. The driver may then find himself crossing through the intersection after the light has changed to red. This simple "risky" decision may be due less to an altered tolerance or preference for risk as much as to a simple error in the assessment of the situation brought about by incomplete or poorly attended sensory information.

Simple lapses of attention can occur following prolonged periods of continuous wakefulness but can also increase in probability following multiple days or weeks where sleep has been curtailed by only a few hours per night (Van Dongen, Maislin, Mullington, & Dinges, 2003). Because the probability of attentional lapses increases whenever sleep is reduced below an individual's optimal range, any behavior that occurs during a sleep-restricted state can be considered as higher risk. Naturally, the magnitude of that risk will depend on the severity of the potential consequences from an attentional failure.

In summary, high-risk behavior is more likely during periods of prolonged sleep loss because the degradation of simple attention increases the probability of making errors or missing critical information.

LACK OF AWARENESS OF DEFICITS

Risk-taking can occur because an individual fails to appreciate the potential hazards associated with their choice or behavior. For example, a person who has consumed several alcoholic beverages may attempt to drive home while intoxicated—an extremely risky activity—simply because the alcohol has affected their ability to judge the severity of their deficits. The behavioral effects of sleep deprivation have been frequently compared to those of alcohol intoxication and shown to produce similar levels of psychomotor impairment (Arnedt, Wilde, Munt, & MacLean, 2001; Dawson & Reid, 1997). In fact, several studies have now shown that the impairment associated with 24 h of total sleep deprivation is comparable to a blood alcohol concentration of approximately 0.10, which equals or exceeds the legal limit in all 50 states in the United States (Dawson & Reid, 1997; Williamson & Feyer, 2000).

Sleep deprivation, however, may actually share more in common with alcohol intoxication than simply an impairment of psychomotor responses. Just as an individual who is legally intoxicated may fail to appreciate the severity of their deficits, some evidence also suggests that sleep-deprived individuals may lack a full awareness of their impairments or level of actual sleepiness. For instance, Van Dongen et al. compared two groups of individuals differing in their objective (i.e., response time) vulnerability to sleep loss during 40 h of total sleep deprivation (Van Dongen, Maislin, & Dinges, 2004). Participants who had been selected to be more vulnerable to sleep loss showed severe increases in the number of attentional lapses during the 40-h vigil, while those selected to be less vulnerable were relatively stable over the same time period. However, despite the obvious differences in objective performance, these two groups reported their subjective sleepiness to be virtually identical on a 7-point sleepiness scale, suggesting that the worst performers were essentially unaware of the true magnitude of their impairment. In other words, an individual's judgment of his/her level of sleepiness is not a reliable indicator of actual performance capacity. On the other hand, some evidence suggests that sleep-deprived individuals are reasonably able to make accurate judgments about their level of performance impairment for various cognitive capabilities (Baranski, 2007; Baranski, Pigeau, & Angus, 1994), suggesting that some aspects of judgment may be more impaired than others. Additional research will be necessary to clarify the extent to which impaired awareness of deficits contributes to risk-taking.

In summary, sleep loss increases risk in some cases by obscuring awareness of the magnitude of deficits in performance.

REDUCED INHIBITORY CAPACITY

Sometimes, behavioral risk-taking can be elevated due to insufficient inhibitory control. Behavioral inhibition requires the ability to judge when a behavior or response is appropriate to a specific context or circumstance, as well as the ability to withhold a response once it is deemed inappropriate or disadvantageous. In the laboratory, inhibitory

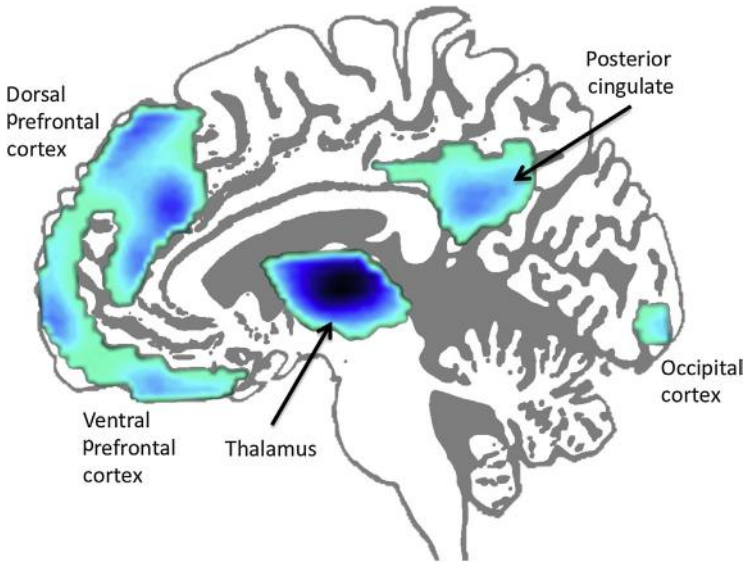

FIGURE 1 Sleep deprivation for 24 h is associated with reduced glucose metabolism (blue regions) within the prefrontal cortex (Thomas et al., 2000). *Courtesy of Maria Thomas, with special thanks to Gregory Belenky of the Walter Reed Army Institute of Research and Henry Halcomb of Johns Hopkins University.*

control is often measured with behavioral tasks such as the "go/no-go" paradigm. While there are many variants of this task, most involve having a participant learn to respond (i.e., "go") to a specific type of stimulus that is presented relatively frequently while learning to withhold responses (i.e., "no-go") to an alternate less frequently presented stimulus. Because the examinee must respond quickly to each stimulus, the frequently occurring "go" trials establish a prepotent response that is difficult to inhibit when the less frequently occurring "no-go" stimulus is encountered. This type of inhibitory paradigm is believed to recruit prefrontal regions of the brain, particularly the right prefrontal cortex (Chuah, Venkatraman, Dinges, & Chee, 2006).

Because sleep deprivation reduces metabolic activity in the dorsolateral region of the prefrontal cortex (Thomas et al., 2000, 2003; Wu et al., 2006; see Figure 1), it has been hypothesized that there should be a corresponding degradation of higher-level executive control capacities (Harrison & Horne, 1999, 2000; Horne, 1988, 1993). In particular, inhibitory control and various forms of go/no-go tasks are believed to rely heavily upon the dorsolateral and ventrolateral prefrontal regions (Liddle, Kiehl, & Smith, 2001). Drummond et al. administered a go/no-go task at multiple time points over a 3-day period of sleep deprivation and showed impaired inhibitory control at 23, 32, and 55 h of sleep deprivation, which returned to normal following a single night of recovery sleep (Drummond, Paulus, & Tapert, 2006). The authors also showed that correct "go" responses—a measure of simple attention and reaction time—were only affected by sleep deprivation after 55 h, suggesting that inhibitory control degraded more rapidly than simple attention (Drummond et al., 2006). Furthermore, older adults (mean age: 68) appeared just as vulnerable to deficits in inhibitory control following sleep deprivation as younger adults (mean age: 23)—a finding that contrasts with the typically greater resistance to sleep loss shown by older individuals on sustained-attention tasks (Sagaspe et al., 2012).

However, other data suggest that time-of-day effects may exacerbate or negate some of the effects of sleep loss on go/no-go performance, with degraded performance most apparent near the circadian nadir in the morning and attenuated near the circadian peak in the afternoon (Bocca, Marie, & Chavoix, 2014). Yet, even after controlling for circadian influences, sleep deprivation still appears to lead to impairment of inhibitory control during an antisaccade test (Bocca et al., 2014) and on the ability to inhibit responses to a pre-established numeric stimulus appearing randomly in a sequence of other digits (e.g., Bratzke, Steinborn, Rolke, & Ulrich, 2012; Harrison, Jones, & Waterhouse, 2007).

In summary, sleep deprivation can increase the potential for risk-taking by impairing the ability to inhibit behavioral responses.

SUBJECTIVE RISK-TAKING PROPENSITY

Some individuals seem to have a preference for high levels of physiological arousal, novel experiences, and the thrill associated with taking risks, a trait known as *sensation seeking* (Hoyle, Stephenson, Palmgreen, Lorch, & Donohew, 2002). A separate but related construct is *risk-taking propensity*, or the willingness and interest in engaging in high-risk activities (Killgore, Vo, Castro, & Hoge, 2006; Sicard, Jouve, & Blin, 2001). Risk-taking behavior may be more probable when either or both of these subjectively rated traits are high. Interestingly, sleep deprivation has been shown to affect scores on measures of both of these risk-related constructs, but in a generally negative direction. Compared to baseline performance, total sleep deprivation was associated with a significant reduction

in scores on measures of self-reported sensation-seeking and self-reported risk-taking propensity after 23 h awake (Killgore, 2007) as well as 46 h awake (Killgore et al., 2008). A different group using the same self-report scale also found reduced risk propensity during a period of overnight sleep deprivation (Chaumet et al., 2009).

The fact that self-rated sensation seeking and risk propensity declined during sleep loss in these studies is not entirely surprising, given that sleep deprivation is commonly associated with increased fatigue and reduced physical and mental energy (Dinges et al., 1997). The data suggest that with greater fatigue, participants seem less interested in activities that would require exertion of effort and high-energy expenditure. A similar decline in self-reported risk-taking propensity was demonstrated in a separate study following 51 h of sleep deprivation (Killgore, Kamimori, & Balkin, 2011). However, after an additional night of sleep loss (i.e., 75 h awake), the trend toward declining risk-taking propensity appeared to reverse. Participants became more interested in risky activities by the third night without sleep, suggesting that risk-taking propensity may show a rebound during periods of extreme sleep deprivation (see Figure 2). It is not clear why this reversal would occur, but some possibilities include an alteration in judgment, increased desire for stimulation due to the boredom of a prolonged stay in the laboratory, or a burst of hypomanic disinhibition due to altered prefrontal functioning. Of particular interest, participants in the same experiment who had received repeated doses of caffeine (200 mg every 2 h) during each preceding night before completing the risk-taking scales appeared to be protected from the surge in subjective risk-taking propensity on the third day, and they continued with lower levels of interest in risky activities than those receiving placebo.

In summary, shorter-term sleep deprivation reduces interest in high-risk sensational activities that require the expenditure of energy, while longer-term sleep deprivation may lead to a resurgence of that interest.

BEHAVIORAL RISK-TAKING

Although a change in risk-related cognitions or attitudes due to sleep loss is important to understand, it is critical to know whether these changes translate into actual alterations in risk-taking behavior. One way to assess this is to administer behavioral tasks that vary in the level of risk of winning or losing something of value. Several sleep deprivation studies that have employed such tasks suggest that the effects of sleep loss on risk-taking behavior are particularly complex.

Cognitive Framing

The effect of sleep loss on risk-taking appears to be influenced by cognitive factors, such as whether the risk is framed as a potential gain or a potential loss. For example, it is well established that most people are risk-avoiding when considering possible gains and risk-seeking when considering possible losses (Kahneman, 2003). Sleep loss appears to alter this basic cognitive bias. Specifically, in one study, when possible outcomes were described in terms of a potential gain, sleep deprivation tended to lead to an increase in risk-taking above baseline; framing the risk in terms of a potential loss tended to lead sleep-deprived individuals

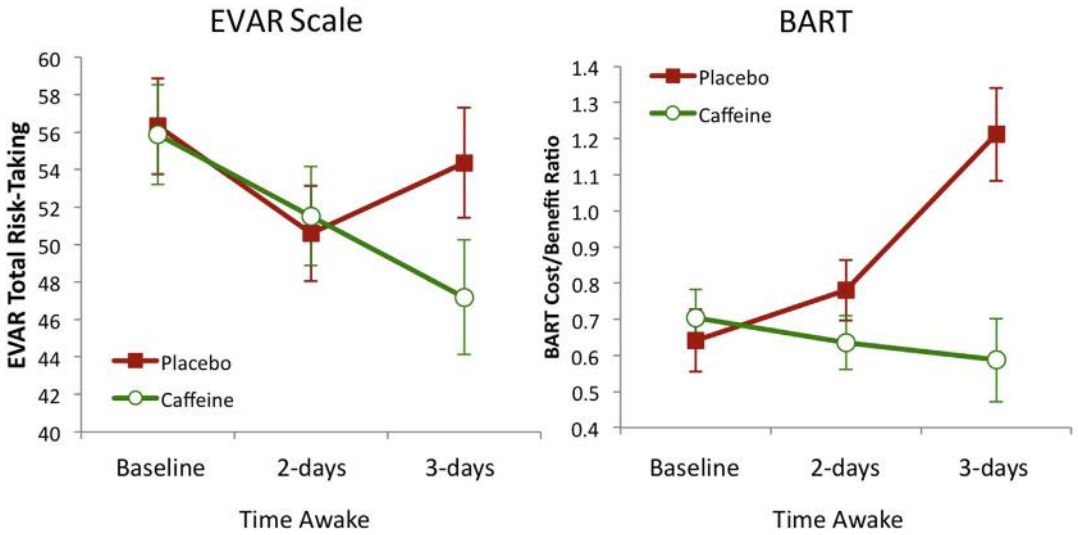

FIGURE 2 The effects of up to 3 days of total sleep deprivation on risk-taking. Left: The placebo and caffeine groups both showed a moderate decline in risk-taking over the first 2 days of sleep deprivation on the Evaluation of Risks (EVAR) scale–English version. The placebo group showed a trend toward a resurgence in total risk scores on the third day, while the caffeine group did not. Right: The placebo and caffeine groups remained stable on the Balloon Analog Risk Task (BART) cost-benefit ratio for the first 2 days, but the placebo group became more risky on the third day without sleep. *Modified from Killgore et al. (2011).*

to become more risk averse than when normally rested (McKenna, Dickinson, Orff, & Drummond, 2007).

In summary, sleep deprivation modifies the framing effect, leading to an increased tendency to take risks when gains are emphasized and the tendency to avoid risks when losses are emphasized.

Altered Expectations

Changes in risk evaluation during sleep loss may be due in part to altered brain functioning within regions that process the values of reward and punishment. Venkatraman, Chuah, Huettel, and Chee (2007) developed a simple roulette-style gambling task for use during functional magnetic resonance imaging. The task presented each participant with several different gambles with outcomes ranging from certain wins to highly risky and uncertain consequences. After only 24 h of sleep deprivation, there were clear increases in brain activation during the risky decisions, including increased activation of the nucleus accumbens, a key structure involved in the anticipation of rewards. This activation could be interpreted as potentially increasing the rewarding value of risky bets during periods of prolonged wakefulness. Moreover, the authors also looked at how the brain processed the experience of losses and found that sleep deprivation significantly attenuated responses in the insular cortex, a region involved in signaling disappointment and visceral signals often associated with negative affect (Venkatraman et al., 2007). The authors interpreted their findings as suggesting that sleep deprivation leads to alterations in brain activation of key reward processing regions that might predispose individuals to risky behavior by increasing the expectation of winning while attenuating the experience of loss.

In a follow-up study, Venkatraman et al. used a complex decision-making task to further clarify the effects of sleep deprivation on the expectation of reward (Venkatraman, Huettel, Chuah, Payne, & Chee, 2011). The task allowed the authors to tease apart how sleep loss affected trials where the focus was on gains versus trials where the focus was on losses. In each gain-focused trial, participants had the option to increase the potential money that could be won or increase the probability of winning the predefined amount. Conversely, during loss-focused trials, participants could either choose to reduce the amount of money that might be lost or reduce the probability that the predefined amount would be lost. When normally rested, participants tended to have a bias toward avoiding losses. However, once they were sleep deprived, this bias shifted toward maximizing gain, a pattern that could lead to increased propensity for risk-taking. Furthermore, this shift in expectation was associated with a reduction in activation of brain regions associated with aversion and negative affect and an increase in regions associated with anticipation of reward (Venkatraman et al., 2011). Such patterns of brain activation would be expected to lead to increased propensity to take risks when sleep deprived.

In summary, sleep deprivation alters functional activation in brain regions associated with reward and aversion, potentially increasing the expectation that risky decisions will lead to gain.

Risky Decision-Making

Whether a decision is risky or safe also depends on the time window surrounding the outcome. Focusing on immediate gains that ultimately lead to long-term losses can be a risky approach. For example, many behaviors such as cigarette smoking, overeating, unprotected sex, or sedentary lifestyle are risky because they involve a long-term trade-off of having poorer health in the future for immediate gratification in the present. A well-studied measure of behavioral risk-taking that assesses this type of risky decision-making is known as the Iowa Gambling Task (IGT). The task is simple and low in effort, requiring participants to try to win money by selecting cards from among four decks with varied, but unspecified, payout schemes. The task assesses relative preferences for choice options that provide volatile, highly exciting, immediate rewards at the possible expense of long-term losses (i.e., "risky" decisions) versus choice options that emphasize more conservative but stable rewards that ensure a more secure long-term outcome (i.e., "safe" decisions). Healthy normal individuals tend to learn to play the IGT with a safe strategy, preferring to maximize long-term profits over short-term gains, while patients with focal brain damage to the ventromedial prefrontal cortex tend to resort to a risky strategy that emphasizes immediate gains but which leads ultimately to financial loss (Bechara, Damasio, Damasio, & Anderson, 1994; Bechara, Damasio, Tranel, & Damasio, 1997).

Several studies have consistently demonstrated that sleep deprivation is associated with a shift in performance on the IGT toward a pattern that is qualitatively similar to that of patients with lesions to the ventromedial prefrontal cortex (Killgore, Balkin, & Wesensten, 2006; Killgore, Grugle, & Balkin, 2012; Killgore, Lipizzi, Kamimori, & Balkin, 2007), showing a pattern of risky behavior that is focused on short-term rather than long-term gains. Across these studies, the pattern of impairment appears to become more severe with longer durations of sleep loss. Moreover, the deficits appear to be unaffected by recent administration of stimulant countermeasures such as caffeine, dextroamphetamine, or modafinil (Killgore et al., 2012; Killgore, Lipizzi, et al., 2007). The failure to normalize functioning on the IGT with stimulants is notable; in each case, performance on simple measures of attention and vigilance was restored to essentially baseline levels. This suggests that the effects of sleep loss on the IGT are likely due to alterations in the decision-making process itself rather than to

simple impairment of attention or vigilance. Furthermore, recent data from our laboratory suggest that sleep loss reduces the psychological weight that subjects give to more temporally distant versus more recent trials on the IGT in their decision-making strategy. In other words, insufficient sleep may affect risk-taking by shortening the "time horizon" from which decision information is integrated into the decision-making process. This could lead to increased risk-taking because decision-makers may fail to consider all relevant data.

In summary, sleep-deprived individuals tend to select riskier options that focus on immediate short-term gains without full consideration of the longer-term consequences of their actions.

Pushing the Limits

Another form of risk-taking involves "pressing one's luck" beyond the point where the benefits of success are outweighed by the costs of failure. A relevant behavioral measure of this type of risk-taking is the Balloon Analog Risk Task (BART), which presents an individual with a series of 30 virtual balloons on a computer screen. To win money on the task, the participant must incrementally inflate each balloon by repeatedly pressing the spacebar on a keyboard. With each subsequent key press, the size and monetary value of the balloon increase by a consistent amount (e.g., 2-mm diameter; 25¢). The larger the diameter of the balloon, the greater its potential monetary value, which can be "banked" at any point by pressing a button to end the trial and keep the accumulated value. However, each balloon also has its own undisclosed and unique breaking point. If a balloon explodes, all accumulated value for that trial is lost and cannot be recouped. Consequently, the key to success on the task is to somehow inflate each balloon as close to its unknown breaking point as possible without exploding it, and then cash in the accumulated value. A commonly used dependent variable from the BART is known as the Adjusted Average Number of Pumps, which is the mean number of key presses for the unexploded balloon trials (i.e., those trials that were "banked" without popping the balloon). An alternative scoring method has also been proposed, the Cost/Benefit Ratio, which takes into account both the Cost (i.e., proportion of exploded balloons) versus the Benefit (i.e., the proportion of all potential money that was actually banked) (Killgore, 2007; Killgore et al., 2008, 2011). Higher scores reflect greater risk-taking (i.e., high cost to low benefit).

The BART has been utilized in a number of sleep deprivation studies, with fairly consistent results. An early study using the BART found that a single night of sleep deprivation was associated with reduced risk-taking (i.e., lower Adjusted Average Number of Pumps) among women but not men (Acheson, Richards, & de Wit, 2007). Killgore explored the effects of one night of sleep loss and also confirmed that participants showed a significant decline in the Cost/Benefit Ratio, suggesting a tendency toward less behavioral risk-taking (Killgore, 2007). This same pattern was found after two nights without sleep, but was reversed by a 20-mg dose of dextroamphetamine, although not by similarly alerting doses of modafinil 400 mg or caffeine 600 mg (Killgore et al., 2008), thus raising the possibility that this stimulant may affect some aspects of risk-taking propensity. Killgore et al. also showed that BART Cost/Benefit scores were unaffected by up to 51 h of sleep deprivation, but this was followed by a surge in behavioral risk-taking by 75 h of wakefulness (Killgore et al., 2011)—an effect that was ameliorated by repeated doses of caffeine 200 mg every 2 h during the overnight period preceding the task (800 mg total per night). Although the cause of this surge in risk-taking after three nights is not clear, it is possible that behavioral inhibition may reach a breaking point following prolonged sleep loss or that participants may have been attempting to self-stimulate to keep themselves alert. This corresponds with the spike in self-reported risk-taking propensity described earlier (Killgore et al., 2011).

One inconsistency in the literature on sleep loss and risk-taking is why sleep deprivation leads to increased risk-taking on the IGT but generally reduced risk-taking on the BART. Killgore et al. have suggested that this inconsistency may be explained simply as a function of the reduced willingness to expend effort during moderate levels of sleep deprivation (Killgore, 2007). Specifically, although the risky options on the IGT require equal effort as the safe options (i.e., a single button press is required regardless of the deck selection), risky behavior on the BART requires the exertion of additional effort (i.e., risky behavior requires in participant to press the spacebar more times). After a period of sleep deprivation, sleepy participants may be inclined to make riskier choices when additional effort is not required (e.g., IGT) but may be too unmotivated to invest additional effort in risk-taking behavior when the safer alternative is less effortful (e.g., BART). Indeed, data suggest that sleep-deprived volunteers engage in "effort discounting"—a willingness to accept rewards of lesser value if only minimal effort is required rather than to expend greater effort to obtain higher value rewards (Libedinsky et al., 2013).

In summary, moderate sleep deprivation appears to reduce the willingness to engage in risky behavior if it requires greater effort or energy expenditure than a less risky alternative. This pattern may reverse at more extreme levels of sleep deprivation.

Aggressive/Punitive Responses

The propensity to respond to frustration or relational discord with aggression can also increase the risk associated with an interpersonal situation. Sleep deprivation appears

to increase the willingness to blame others for difficult circumstances and reduces the willingness to try to smooth over the interpersonal problems or consider mutually satisfying outcomes (Kahn-Greene, Lipizzi, Conrad, Kamimori, & Killgore, 2006). This is consistent with laboratory findings showing that sleep loss increases the propensity toward suspicious paranoid thinking and feelings of persecution by others (Kahn-Greene, Killgore, Kamimori, Balkin, & Killgore, 2007). Further evidence suggests that sleep deprivation may reduce the ability to inhibit aggressive behaviors (Kamphuis, Meerlo, Koolhaas, & Lancel, 2012). One study examined how sleep-deprived subjects behaved during a series of "bargaining" and "trust" games that involved interactions with other players and that had real financial consequences (Anderson & Dickinson, 2010). Sleep deprivation increased the likelihood that participants engaged in some form of aggressive exchange with the other players. In particular, sleep-deprived individuals reported lower trust of their partners and were more likely to reject monetary offers that were perceived as unfair, even if doing so came at a financial loss to themselves.

In summary, sleep deprivation may elevate risk by increasing mistrustful and aggressive personality tendencies and impairing the willingness to engage in prosocial behavior.

Moral Judgment

Within a given social system, an individual's moral perspectives will dictate many of his or her behaviors and decisions. Moral beliefs that fall outside of the norms of a particular social group or culture will probably lead to behavior that will be sanctioned or punished within that group. Thus, the quality and form of moral judgments are likely to affect behavioral risk-taking. Several studies have shown that the processing of moral information can be particularly disrupted by sleep loss.

In the first study to examine moral judgment following sleep loss, participants completed a series of moral and nonmoral dilemmas when normally rested and again following 53 h of sleep deprivation (Killgore, Killgore et al., 2007). Compared to normally rested performance, sleep deprivation was associated with significant slowing of moral decisions involving highly emotionally charged personal involvement, but had virtually no effect on moral judgments with low personal involvement or neutral control dilemmas that were devoid of moral and emotional issues. This was interpreted as evidence that sleep loss selectively disrupts the ability to resolve highly emotionally charged cognitive conflicts more than other types of decisions. Furthermore, sleep-deprived participants were more prone to make utilitarian-type judgments that violated their own moral beliefs than when normally rested (Killgore, Killgore et al., 2007). This effect was not observed in a second study of only a single night of sleep loss (Tempesta et al., 2012), suggesting that the duration of sleep deprivation may be an important variable in studies of moral judgment.

Interestingly, partial sleep restriction may also be sufficient to induce alterations in moral reasoning. One study showed that restricting sleep to approximately 2.5 h per night for 5 days reduced principle-oriented moral reasoning among trainees engaged in a military exercise (Olsen, Pallesen, & Eid, 2010). Moral decisions among these military cadets became more rules-focused and self-oriented during the period of sleep restriction. The cadets also became increasingly unable to engage in higher-level principle-oriented reasoning as wakefulness was extended. While that study did not examine how moral judgments were ultimately implemented into potentially risky behaviors, it is not difficult to see the potential connection and how such changes in cognition could lead to increases in high-risk activities. This important topic deserves further research.

In summary, sleep deprivation alters the speed and quality of judgments made in response to difficult moral dilemmas, which could potentially affect the willingness to engage in behavior that would place some parties at greater risk.

CONCLUSIONS

Lack of sleep appears to have many complex effects on the brain and behavior, which may ultimately contribute to greater risk-taking propensity. From an elementary cognitive perspective, sleep loss impairs simple attentional processes, making them more variable and unstable. This instability of attention can elevate the level of risk inherent in almost any activity simply by impairing an individual's situational awareness and increasing the likelihood of mistakes. Simply put, an inattentive individual is a risky individual. Sleep loss also alters the ability to appreciate the severity of these deficits in attention and the accompanying impairments in psychomotor performance, which can lead a person to take inappropriate risks due to impaired judgment. Just as alcohol can increase risk by impairing judgment, insufficient sleep can do the same.

Risk-taking can also be increased by insufficient sleep because it reduces the ability to inhibit inappropriate behaviors. Without appropriate inhibitory control, an individual may unintentionally behave in ways that cause errors, harm, or even evoke risky punitive sanctioning responses from others. Interestingly, most people report reduced interest in sensation-seeking and high-risk activities when sleep deprived, yet make decisions that often favor higher-risk choices. Some of this appears to involve changes in brain and cognitive systems that ultimately bias individuals toward favoring risky options while minimizing the perceived negative consequences of their actions. Sleep deprivation is also associated with a tendency to focus on the immediate short-term

consequences of behavior while de-emphasizing longer-term outcomes, a pattern that can increase risky decisions. Interestingly, this type of risk preference only appears to be manifested when the effort required to follow the high-risk option is minimal. When a risky choice requires more effort than a safer option, sleep-deprived individuals seem to avoid exerting themselves. Finally, sleep loss also affects emotional responses to frustrating situations, which in itself may increase risky behavior by elevating the tendency to blame others, act aggressively, and even make different moral decisions than when normally rested.

Although the research base on this topic is still in its infancy, the overwhelming evidence thus far points to a robust effect of sleep loss on risk-related cognition and behavior.

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Part VI

Food, Nutrients, and Dietary Supplements: Sleep Modulation

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Chapter 31

Relation between Magnesium Deficiency and Sleep Disorders and Associated Pathological Changes

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Chapter Outline

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INTRODUCTION

Magnesium is the second most abundant cation in intracellular fluid and the fourth most abundant mineral element in the brain. Magnesium is needed for more than 300 enzyme reactions, including those used for neurotransmitter synthesis, and is involved in cholinergic, monoaminergic, and amino acid neurotransmitter function. Thus, magnesium has a key role in the regulation of central nervous system (CNS) excitability. Quantitative electroencephalogram (EEG) analysis of experimentally magnesium-deprived humans has shown that magnesium deficiency induces CNS hyperexcitability (Penland, 1995). Because neurological changes such as hyperexcitability result in sleep disorders, magnesium can be considered a modulator of sleep quality. Impairment of this modulation by magnesium deficiency may be a significant contributor to the high incidence of sleep disorders, which can lead to adverse health consequences.

MAGNESIUM DEFICIENCY IN HUMANS

Reliable status indicators and balance data were lacking for the determination of the current Dietary Reference Intakes (DRIs) for magnesium when they were set in 1997 (Food and Nutrition Board, Institute of Medicine, 1997). Estimated Average Requirement (EAR; intake at which 50% of population is deficient) and Recommended Dietary Allowance (RDA; meets the requirement of 98% of healthy people) were based on very variable balance data from 34 men and women on self-selected diets that decreased in magnesium during the balance periods. Some subjects on magnesium intakes less than 258 mg/day were in positive balance, and some subjects on intakes greater than 299 mg/day were in negative balance. This resulted in EARs and RDAs for men (330–350 and 410–420 mg/day) and women (255–265 and 310–320 mg/day) that have been questioned by expert panels and resulted in suspect assessments on the extent of dietary magnesium deficiency that could cause health concerns such as sleep disorders. Since 1997, balance data have been reported that apparently give a more accurate approximation of DRIs. In one study, pooled data from 27 different tightly controlled metabolic unit studies that included 150 women and 93 men indicated neutral magnesium balance at an intake of 165 mg/day (Hunt & Johnson, 2006). This intake may be near the EAR for normal healthy adults eating a diet otherwise adequate in needed nutrients. The 95% prediction intervals were 113 and 237 mg/day, which suggest an RDA modestly higher than 237 mg/day.

Survey data (Moshfegh, Goldman, Ahuja, Rodes, & LaComb, 2009) from the 2005–2006 National Health and Nutrition Examination Survey (NHANES) indicated that the usual magnesium intake from food of about 60% of all adults did not meet the magnesium RDAs set in 1997 that recent balance data suggest are too high. However, the survey data also indicated that 10% of adults older than 19 years have magnesium intakes from food and water that

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are about 50% of the 1997 RDAs. This translates into about 155–165 mg/day for women and 205–210 mg/day for men, which are intakes that likely would be considered deficient even if lower EARs and RDAs are eventually set. In addition, the survey data indicated that more than 25% of adults would not meet the suggested lower magnesium RDA of modestly higher than 237 mg/day. In a study involving 224 postmenopausal women, three 5-day food diaries found that 38% had regular magnesium intakes less than 237 mg/day (Nielsen, Lukaski, Johnson, & Roughead, 2011). In another study involving 22 men and 78 women older than 51 years with poor sleep quality, 37% had serum magnesium concentrations below 1.8 mg/dL (0.74 mmol/L), an indication of subclinical magnesium deficiency (Nielsen, Johnson, & Zeng, 2010). Thus, dietary magnesium deficiency such that it would affect sleep quality in humans may be a common occurrence, especially in older adults.

Even with a magnesium intake that meets an RDA, deficiency may occur because of increased need caused by numerous factors that impair absorption or increase excretion of magnesium (Rude & Shils, 2006). Among the factors that impair absorption are malabsorption syndromes, chronic diarrhea, and bariatric surgery. Numerous drugs or medications are a significant cause of increased need for magnesium. For example, diuretics cause marked renal magnesium wasting and proton pump inhibitors apparently decrease magnesium absorption. Alcohol is a drug that probably has a major impact on the occurrence of magnesium deficiency. Decreased serum magnesium concentrations are commonly found in alcohol-dependent people. Among the factors responsible for the decreased magnesium status with alcohol abuse is a reduced intake resulting from a poor diet, increased tubular excretion caused by renal tubular dysfunction, and increased urinary loss because of reduced antidiuretic hormone levels.

Renal magnesium loss can also be caused by metabolic or endocrine disorders such as diabetes, hyperparathyroidism, and aldosteronism. In addition, chronic renal tubular, glomerular, or interstitial diseases are often associated with renal magnesium wasting.

Interestingly, chronic stress that included sleep deprivation was found to decrease erythrocyte magnesium and this was accompanied by an increase in plasma epinephrine; these changes were accompanied by an increase in heart rate variability (Takase et al., 2004). These changes suggest that sleep deprivation may decrease magnesium status. Another consequence of sleep deprivation that is accompanied by decreased erythrocyte magnesium and altered catecholamine secretion is decreased exercise tolerance (Tanabe et al., 1998). When eight subjects received an oral dose of 100 mg of magnesium daily and another eight were untreated for 1 month, the ratio of erythrocyte magnesium between the sleep-deprived state (sleep time up to 60% less than usual for 1 month) and usual good sleep state was significantly higher in the magnesium-supplemented than in the unsupplemented group. The magnesium-supplemented subjects did not show any differences between the sleep-deprived and sleep-normal periods in anaerobic threshold and peak oxygen uptake during an exercise tolerance test. The untreated controls exhibited a decrease in both of these variables during the sleep-deprived versus sleep-normal periods. Plasma norepinephrine was increased during the exercise peak after chronic sleep deprivation in the magnesium-supplemented group but not in the untreated group. The preceding findings suggest that sleep deprivation may have a negative impact on magnesium metabolism and perhaps increase the need for magnesium. This would result in a relative magnesium-deficient status, which may be responsible for some of the consequences of the sleep deprivation.

BIOCHEMICAL BASIS FOR MAGNESIUM AFFECTING SLEEP

A review by Turner and Vink (2006) indicates that increasing extracellular magnesium can enter cerebrospinal fluid and increase brain intracellular free magnesium concentration, which influences a number of intracellular processes, including receptor activity such as the N-methyl-D-aspartate (NMDA) receptor. Magnesium deficiency has been shown to decrease the CNS magnesium concentration in animal models. For example, compared to rats fed 980 mg magnesium/kg diet, rats fed 35 mg magnesium/kg diet for 10 days had significantly lower magnesium concentrations in the cerebrospinal fluid (0.78 ± 0.07 vs 0.94 ± 0.05) and in the spinal cord (5.49 ± 0.07 vs 6.09 ± 0.06) (Alloui et al., 2003). Magnesium-loading the deficient rats restored the magnesium concentrations to levels not significantly different than controls in two days. Traumatic brain injury also has been shown to significantly decrease brain magnesium 40–60%, which exacerbated neurological deficits, but the decline was never found to decrease below 0.2 mM (Turner & Vink, 2006). Apparently, this is a threshold below which the ion cannot fall under physiological conditions. Thus, changes in CNS biochemical mechanisms induced by magnesium deficiency could be a basis for a relationship between magnesium and sleep.

A biochemical mechanism through which magnesium can affect sleep architecture is through the modulation of ligand-gated ion channels, especially the NMDA and γ-amino butyric acid (GABA) receptor systems. The NMDA receptor is a glutamate-gated voltage-dependent ion channel blocked by extracellular magnesium at resting membrane potentials. A reduction in the blockade by magnesium deficiency resulting in enhanced activation of the NMDA receptor can increase cell permeability for calcium ions and neuronal activity in the brain. Increased activation of NMDA receptors apparently occurs with poor sleep

architecture. For example, slow-wave sleep was increased in animal models after the administration of NMDA antagonists (Campbell & Feinberg, 1996; Held et al., 2002; Juhasz, Kekesi, Emri, Soltesz, & Crunelli, 1990). On the other hand, magnesium can potentiate GABAergic signaling (Horne, Harrison, Turner, & Simmonds, 1986; Schwartz, Wagner, Yu, & Martin, 1994). GABA agonists have been found to increase slow-wave sleep in humans (Faulhaber, Steiger, & Lancel, 1997). Many sleep medicines act through augmenting the GABA system.

Another mechanism through which sleep may be affected by magnesium is through an effect on monoamine metabolism. Magnesium deficiency (50 mg magnesium/kg diet for 40 days) was found to increase cerebral dopamine and 5-hydroxy-indole-3-acetic acid compared to magnesium-adequate rats (1.0 g magnesium/kg diet), and this rise was accompanied by an increase in wakefulness and a decrease in sleep percent in rats (Poenaru et al., 1984). The basis for this increase in dopamine and serotonin metabolites in magnesium deficiency has not been clearly established.

MAGNESIUM DEFICIENCY AND SLEEP DISORDERS

Studies with animal models have indicated that a decreased magnesium status results in poor sleep organization. Sleep analysis of two lines of mice selected for low and high erythrocyte magnesium levels found that the amplitude of daily variation in sleep and slow-wave sleep delta power was markedly decreased in those with high erythrocyte magnesium (Chollet et al., 2001). Rats fed a magnesium-deficient diet (200 mg/kg) for six weeks exhibited increased neuronal excitability and a significant increase in wakefulness at the expense of slow-wave sleep when compared to controls fed 500 mg magnesium/kg diet (Depoortere, Francon, & Llopis, 1993). Feeding the deficient rats a diet with adequate magnesium for two weeks restored sleep organization to original patterns.

Human studies have shown that a low magnesium status is associated with sleep dysfunction, or that magnesium supplementation improves sleep quality. An evaluation of 1320 patients found 397 with decreased serum and erythrocyte magnesium concentrations; 240 of the 397 suffered from nocturnal insomnia (Popoviciu et al., 1991). Polysomnographic recordings from 35 of the magnesium-low patients with insomnia revealed an increase in sleep latency, predominance of light slow-wave sleep, diminution of deep slow-wave sleep and a reduction in rapid eye movement (REM) sleep. In infants, serum magnesium concentrations were correlated with sleep behavior (Dralle & Boedeker, 1980). With increasing serum magnesium, quiet sleep increased while active sleep decreased. An injection with magnesium further increased quiet sleep and decreased active sleep. In a study involving 100 adults older than 51 years with poor-quality sleep, both a magnesium citrate supplement providing 320 magnesium and a sodium citrate placebo daily for seven weeks significantly increased erythrocyte magnesium; both treatments also significantly improved sleep as assessed by the Pittsburg Sleep Quality Index (Nielsen et al., 2010).

Aging is often accompanied by a decline in sleep continuity, shortening of REM latency, decreased slow-wave sleep, and increased nocturnal wakefulness (Held et al., 2002). It is thought that this disordered sleep is not caused by aging per se, but by factors associated with aging. As indicated above, the population group very susceptible to magnesium deficiency is the elderly. Thus, magnesium deficiency might be contributing to the occurrence of disordered sleep in older individuals. This suggestion is supported by a study in which 12 subjects aged 60–80 years were supplemented with a creeping dose of magnesium over 20 days ending with a dose of 30 mmol (729 mg)/day for 14 days in a placebo-controlled, randomized crossover designed experiment. The treatment significantly increased slow-wave sleep (Held et al., 2002). The treatment also reversed some neuroendocrine changes found in elderly subjects, which occurred in the hypothalamic–pituitary–adrenal and the renin–angiotensin–aldosterone systems. Magnesium supplementation increased nocturnal renin and aldosterone secretion and decreased cortisol secretion. Similar findings were obtained in a double-blind clinical trial in which elderly subjects were randomly allocated to a placebo or 500 mg magnesium daily for 8 weeks (Abbasi et al., 2012). Although the serum magnesium concentrations of the subjects were in the normal range (>0.75 mmol/L), dietary magnesium intake was determined to be quite low (~194 mg/day). The magnesium supplementation resulted in significant increases in sleep time, sleep efficiency, and serum renin and melatonin concentrations, and decrease in insomnia severity index score, sleep onset latency, and serum cortisol concentration.

As described above, alcohol can result in magnesium deficiency, which apparently can persist during subacute alcohol withdrawal. Alcohol-dependent people, even during subacute withdrawal, frequently exhibit sleep disturbances including reduced sleep time, reduction or loss of slow-wave sleep, and increased periodic leg movements. Magnesium supplementation (30 mmol (729 mg)/day for 4 weeks) of 11 such people significantly decreased sleep onset latency and significantly improved subjective sleep quality, as assessed by the Pittsburgh Sleep Quality Index (Hornyak, Haas, Veit, Gann, & Reimann, 2004).

Because magnesium deficiency can result in neuromuscular hyperexcitability, it is not surprising that some studies have found that magnesium deficiency has been associated with sleep disturbances caused by periodic limb movements or restless leg syndrome. In one study of 10 magnesium-deficient subjects with restless leg syndrome,

neuromuscular hyperexcitability and some modification in neuromuscular conductivity was found (Popoviciu et al., 1993). These subjects exhibited disordered sleep characterized by agitated sleep with frequent periods of nocturnal awakenings, increased duration and percentage of light slow-wave sleep, and decreased duration and percentage of deep slow-wave sleep and REM sleep. The associative findings do not allow for the determination of whether magnesium deficiency was the cause or effect of the restless leg syndrome. However, a magnesium intervention study suggests that magnesium deficiency may have been responsible for the neuromuscular changes and restless legs. In this study of 10 subjects with insomnia caused by these limb movements, a daily evening oral dose of 12.4 mmol (301 mg) of magnesium for 4–6 weeks significantly reduced arousals associated with limb movements and increased sleep efficiency (Hornyak, Voderholzer, Hohagen, Berger, & Riemann, 1998).

Magnesium deficiency may also be involved in the etiology of some parasomnias. Marked hypomagnesemia (0.69 mmol/L) was found in 27 patients identified as having various parasomnias (night terrors, nocturnal motor automatisms, nocturnal verbal automatisms, sometimes with bruxisms) in a group of 397 patients (Popoviciu et al., 1990). These subjects exhibited severe sleep disorders with EEG abnormalities occurring during slow-wave sleep.

Magnesium Deficiency, Inflammation, and Sleep-Associated Pathological Disorders

Sleep quality may have an impact on the genesis of disease because even modest sleep loss may increase markers of inflammatory stress, which is considered to increase the susceptibility to chronic diseases such as atherosclerosis and diabetes. In addition, sleep dysfunction reportedly exacerbates numerous pathological disorders characterized as having increased inflammatory stress (Ali, Choe, Awab, Wagener, & Orr, 2013).

Cross-sectional analysis of 5003 middle-aged women and men found that shorter sleep time was associated with higher levels of the inflammatory markers interleukin 6 (IL-6) and C-reactive protein (CRP) (Ferrie et al., 2013). This finding was consistent with findings in an earlier study; plasma levels of the inflammatory cytokines IL-6 and tumor necrosis factor-α (TNF-α) were elevated in patients with sleep apnea and narcolepsy (abnormalities in sleep stage sequencing) that caused excessive daytime sleepiness (Vgontzas et al., 1997). The highest elevations were found in the sleep apnea group, which also had the highest body mass index (BMI). Animal and human studies indicate that IL-6 secretion is positively regulated by catecholamines through β-adrenergic receptors. Increased peripheral sympathetic activity, which is found in sleep apnea and obesity, might be the inducer of increased IL-6.

Many pathological conditions associated with magnesium deficiency have been characterized as having a chronic inflammatory stress component, including diabetes and cardiovascular disease (Nielsen, 2010). Several studies have found that magnesium intake is inversely associated with chronic inflammatory stress characterized by elevated serum or plasma CRP (Nielsen, 2010). An analysis of 1999–2002 NHANES data from 5773 adults, after controlling for age, race, gender, BMI, smoking, income, alcohol consumption, exercise, medical conditions, and total caloric intake, found that those over the age of 40 years with a BMI > 25 and consuming less than 50% of the RDA for magnesium were 2.24 times more likely to have elevated serum CRP than adults consuming ≥RDA (King, Mainous, Geesey, & Woolson, 2005). A linear regression analysis of 3173 postmenopausal women aged 50–79 years in the Women's Health Initiative Observational Study found that magnesium intake was inversely associated with CRP, TNFα-R2, and IL-6 after adjustment for age, ethnicity, clinical center, time of blood draw, smoking, alcohol, physical activity, energy intake, BMI, and diabetes status (Chacko et al., 2010).

Further evidence of a relationship among magnesium deficiency, inflammatory stress, and poor sleep is provided by obese individuals. Numerous experimental, epidemiological, and clinical studies have indicated that chronic low-grade inflammation and abnormal cytokine production, increased acute-phase reactants, and activation of inflammatory signaling pathways are involved in obesity-related disease development, including type 2 diabetes and atherosclerosis (Hotamisligil, 2006). Obesity frequently is associated with subjective complaints of fatigue, excessive daytime sleep, and nocturnal sleep disturbances, as well as a higher degree of objective excessive daytime sleepiness than in age- and sex-matched controls (Vgontzas et al., 1998, 1994). As indicated above, excessive daytime sleepiness and fatigue have been associated with increased plasma cytokines (Vgontzas et al., 1997). Several studies have indicated that a low magnesium status in obesity is associated with chronic inflammation markers, or with diseases with a chronic inflammation component (Nielsen, 2010). A low magnesium status apparently occurs more often in obese than in nonobese individuals. For example, in a cross-sectional population-based study that included 192 nondiabetic nonhypertensive subjects, the mean serum magnesium concentration of 52 subjects with a BMI of <25.0 was 0.83 mmol/L, of 52 subjects with a BMI of ≥25 and <30 was 0.81 mmol/L, and of 52 subjects with a BMI >30 was 0.67 mmol/L (Rodríguez-Moran & Guerrero-Romero, 2004). A serum magnesium concentration below 0.75 mmol/L is generally considered an indication of magnesium deficiency. A possible reason for the finding of low serum magnesium in obese individuals is a low dietary intake. In the International Study of Macro-/Micronutrients and Blood

Pressure (INTERMAP), data from 1794 Americans showed that magnesium intake decreased from 150.9 mg/1000 kcal in men with a BMI <25.0 to 138.1 mg/1000 kcal with a BMI ≥30.0; in women, the decrease was from 155.7 to 133.7 mg/1000 kcal (Shay et al., 2012). The preceding findings support the suggestion that magnesium deficiency may contribute to the occurrence of chronic inflammatory stress and associated poor-quality sleep in obesity.

SUMMARY/CONCLUSION

Magnesium influences neurophysiologic and neuroendocrine mechanisms involved in sleep. Biochemical bases for the influence are the modulation of the NMDA receptor, and perhaps through affecting monoamine metabolism. Magnesium deficiency impairs these actions and thus could negatively affect sleep quality. Because magnesium deficiency commonly occurs, it may be a significant factor in the occurrence of sleep disorders. Support for this statement is the finding that indicators of magnesium deficiency often occur in individuals with sleep disorders. Because magnesium deficiency can induce inflammatory stress, which is also found in sleep-deprived individuals, impaired magnesium utilization or magnesium deficiency may be responsible for some of the pathological consequences of sleep deprivation, such as contributing to the onset of insulin resistance, type 2 diabetes, and cardiovascular disease (Crispim et al., 2007; Nielsen, 2010). Improving magnesium status through increased dietary intake or supplementation may be a treatment that improves sleep quality in individuals with sleep disorders. This action might be a particularly important consideration for older adults, obese individuals, and alcohol abusers, who are often found to be magnesium deficient.

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Chapter 32

Physical Activity and Sedentary Time in Sleep Apnea and Obesity

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Chapter Outline

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PHYSICAL ACTIVITY

Physical activity in its broader sense is defined as "any bodily movement produced by skeletal muscles that results in energy expenditure" (p. 126, Caspersen, Powell, & Christenson, 1985) and thus incorporates both physical activities in daily life (e.g., household chores and active transport) and planned physical exercise. Physical activity enhances our oxygen uptake and muscle strength and has been proven to reduce the risk of cardiovascular diseases through, for example, lowered blood pressure and enhanced stroke volume of the heart (Thompson et al., 2003). Since physical activities increase energy expenditure, physical activity is a vital component in the prevention and treatment of overweight conditions. According to recommendations, all healthy adults should engage in both aerobic activities and muscle-strengthening exercises in order to promote health and prevent diseases. A weekly total of 75 min of vigorous physical activity or 150 min of moderately intense aerobic activity has been recommended (Haskell et al., 2007). Physical activity is recommended to be performed preferably every day of the week and in bouts of at least 8–10 min (Haskell et al., 2007). One hundred and fifty minutes equals 30 min 5 days a week. Expressing this physical activity recommendation in terms of steps, 30 min of moderate physical activity corresponds to about 3000 steps (Tudor-Locke et al., 2011).

PHYSICAL ACTIVITY IN SLEEP APNEA AND OBESITY

Obstructive sleep apnea syndrome (OSAS) and obesity are closely linked in that weight gain increases the risk of OSAS (Peppard, Young, Palta, Dempsey, & Skatrud, 2000) and, likewise, weight loss relieves OSAS severity (Tuomilehto, Seppa, & Uusitupa, 2013). Interestingly however, studies have reported positive effects on OSAS symptoms by regular physical activity or exercise, even without weight loss or other anthropometric changes (Giebelhaus, Strohl, Lormes, Lehmann, & Netzer, 2000; Kline et al., 2011; Netzer et al., 1997; Sengul, Ozalevli, Oztura, Itil, & Baklan, 2011). One explanation for this positive effect is that physical activity enhances the respiratory drive through improved chemoreceptor sensitivity (Hargens et al., 2009) and enhances muscle tone in the upper airway (Giebelhaus et al., 2000). Another hypothesis concerns the elevated levels of inflammatory cytokines in both OSAS and obesity. Since physical activity seems to alter cytokine quantity and profile (Santos, Tufik, & de Mello, 2007), this might be a piece of the puzzle.

Thus, physical activity seems to be an important addition to the treatment of both OSAS and obesity, and therefore it is of great concern to facilitate for these populations to become more physically active. In order to prevent weight gain or to lose weight, it is recommended to accumulate twice the amount of physical activity mentioned above

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(O'Donovan et al., 2010), that is, the equivalent of 60 min of moderately intense aerobic activities 5 days a week. In several observational studies, increasing body mass (Hagströmer, Oja, & Sjöström, 2007; Orsini et al., 2008; Tudor-Locke, Brashear, Johnson, & Katzmarzyk, 2010) has been correlated with lower levels of physical activity. In persons with OSAS, a daily total median of 55 min of moderate to vigorous physical activity has been described (Verwimp, Ameye, & Bruyneel, 2013), that is, numbers close to the recommended amount of activity. However, when analyzing physical activity in bouts of 10 min (i.e., the minimally recommended duration of physical activity), a lower daily mean of 37 min has been reported (Igelström, Emtner, Lindberg, & Åsenlöf, 2013a). These numbers elucidate a need for enhancement in physical activity—at least if the aim is weight loss. Additionally, cardiorespiratory fitness in itself is an important health promotion factor. Among both men (McAuley et al., 2012) and women (Farrell, Finley, McAuley, & Frierson, 2011), a high level of cardiorespiratory fitness seems to protect from serious diseases regardless of body mass index (BMI, kg/m^2) or percent body fat.

SEDENTARY TIME

In recent years it has been highlighted that the current physical activity recommendations are not enough. Research in inactivity physiology has shown that prolonged and uninterrupted sedentary time, such as sitting, has detrimental effects on metabolic risk variables such as waist circumference, triglycerides, and plasma glucose (Healy et al., 2008). Among people with OSAS, a daily average of 8–9 h of lying down has been reported (Diamanti et al., 2013; Verwimp, et al., 2013) and another study has reported a daily mean of 9 h 55 min spent while sedentary during waking time (Igelström, et al., 2013a). Both of these numbers surpass the corresponding numbers in the general population, averaging 7 h 39 min a day (Hagströmer, et al., 2007).

It has been shown that during prolonged muscular inactivity, the level of the enzyme lipoprotein lipase (LPL) is reduced. LPL is crucial for the hydrolysis of the triglycerides contained in lipoproteins, and when LPL is reduced, this hydrolysis process is hampered (Hamilton, Hamilton, & Zderic, 2004). However, the negative effects of prolonged inactivity might be counteracted by regular breaks in sedentary activities (Hamilton, Healy, Dunstan, Zderic, & Owen, 2008), e.g., standing up at regular intervals. In addition, such low-intensity physical activities are important due to higher energy expenditure than various sedentary behaviors, thus, in the long run, being an important factor for weight loss (Elbelt et al., 2010). In a small repeated-measures study of 10 office workers, 3 h of standing-based office work was associated with positive blood glucose responses and 174 kcal higher energy expenditure, compared to sitting (Buckley, Mellor, Morris, & Joseph, 2014). Regarding breaks in sedentary time, after a small study of Japanese women, Ayabe et al. (2013) concluded that the frequency of bouts of 1 min and 3 min (but not 32 s) was inversely associated with the amount of visceral adipose tissue, indicating a positive impact on metabolic parameters of frequent, but not too short, breaks in sedentary time. However, in order to set up recommendations on reduced and interrupted sedentary time, more research is needed on required frequency and duration of interruptions and on interventions regarding behavior change in sedentary time.

CORRELATES OF PHYSICAL ACTIVITY AND SEDENTARY TIME

Having a condition like obesity or OSAS might impose several factors influencing engagement in physical activity. First, it has been reported that persons with OSAS often have a low aerobic capacity (Aguillard, Riedel, Lichstein, Johnson, & Noe, 1998; Ucok et al., 2009) and in obese individuals with very low maximum oxygen uptake, physical activities entail a higher relative oxygen cost, leading to an augmented perceived exertion (Mattsson, Evers Larsson, & Rössner, 1997). Second, in persons with severe OSAS, anomalous hemodynamic responses to submaximal exercise have been observed (Alameri, Al-Kabab, & BaHammam, 2010) that may propel dyspnea perception and perceived exertion. Further, daytime sleepiness, a common symptom of sleep apnea, has been correlated with lower levels of physical activity (Chasens, Umlauf, & Weaver, 2009).

In addition to physical or medical correlates, there are several social, cognitive, and emotional aspects that may hamper physical activity engagement in any individual. According to a population study in the European Union, work/studies were one of the most common perceived barriers for physical activity, as was a perception of not being a sporty type of person (Zunft et al., 1999). In individual interviews, patients with OSAS and obesity have expressed how previous negative experiences of physical activity may hinder physical activity (Igelström, Martin, Emtner, Lindberg, & Åsenlöf, 2012). They also perceived feelings of not fitting in, e.g., at a health club, as a barrier and that it is important that the physical activity feel safe and suitable to the individual's prerequisites. In patients with pain in weight-bearing joints, non-impact activities, such as aerobics without jumps, or non-weight-bearing activities, such as swimming or cycling, are usually recommended. Even though inclining BMI has been reported to increase the risk of injury, especially lower-body musculoskeletal injuries, it is important to bear in mind that this risk has been attributed to body mass rather than exercise engagement (Janney & Jakicic, 2010). Nevertheless, *fear* of injury seems to be an important correlate of physical activity, since this aspect has been reported to predict physical activity

two years after bariatric surgery (Wouters, Larsen, Zijlstra, van Ramhorst, & Geenen, 2011).

Regarding correlates of sedentary time, research is still in its early stages and there is yet much to discover. In young adults it has been reported that depressive symptoms predict sedentary behavior in terms of TV viewing and computer use (Brunet et al., 2014). Among persons with OSAS and overweight, fear of movement (or activity avoidance) seems to play a role in amount of time spent while sedentary (Igelström, Emtner, Lindberg, & Åsenlöf, 2013b).

HEALTH BEHAVIOR CHANGE OF PHYSICAL ACTIVITY AND SEDENTARY TIME

Enhancing physical activity, reducing sedentary time, and initiating interruptions in prolonged muscular inactivity all demand behavioral changes of the individual. Since theories relating to health psychology underline social, emotional, and cognitive determinants of behavior change, it is hypothesized that treatments aiming at behavior change will benefit from attending to these aspects (Knittle, de Gucht, & Maes, 2012). In addition, since behavior change is a learning process, the behavior may be moderated by conditioning (Baldwin & Baldwin, 2001), by its antecedent cues and consequences (Skinner, 1969), by observational learning, and by internal mental states (Bandura, 1977).

For a behavioral change to succeed, it seems to take motivation (or intention), self-regulatory skills (e.g., goal setting, action planning, self-monitoring of behavior), and self-efficacy for initiating and maintaining the new behavior (Gardner, Cane, Rumsey, & Michie, 2012). Even though an individual has a high motivation for physical activity behavior change and many positive outcome expectations, the perceived barriers for physical activity may be ample and the physical activity level low. Self-regulation comprises the individual's "efforts to avoid spontaneous learned, habitual, or innate responses to situational cues and to act in an intentional way" (p. 566, Sniehotta, Schwarzer, Scholz, & Schüz, 2005). Interventions combining different self-regulating behavioral change techniques, such as self-monitoring of behavior, action planning, or time management, have been reported significantly more effective in enhancing physical activity than other interventions (Michie, Abraham, Whittington, & Mc Ateer, 2009; Williams & French, 2011). In addition, an increase in an individual's self-efficacy for physical activity may have positive impact on the physical activity level of that person. Self-efficacy may be addressed, for example, through mastery experiences (e.g., by gradually increasing physical activity and modifying physical activity goals depending on attainments) or by modeling or vicarious experience (e.g., seeing someone succeed with a physical activity behavior). In an intervention trial among inactive aging adults with overweight, increased self-efficacy for physical activity through mastery experiences was reported to directly mediate enhancement in physical activity (Smith Anderson Bill, Winett, Wojcik, & Williams, 2011).

Regarding strategies for reducing sedentary time, additional behavior change trials are needed in order to elucidate effective intervention techniques. In persons with insufficient physical activity, high amounts of sedentary time, and unfavorable intake of saturated fat, fruit, and vegetables, Spring et al. (2012) compared two types of interventions: one focusing on increasing physical activity and lowering intake of saturated fat and the other addressing sedentary time and intake of fruit and vegetables. The results favored the latter; that is, by targeting sedentary time and intake of fruit and vegetables, not only did these two behaviors improve but the participants also increased their amount of physical activity and reduced their intake of saturated fat. Thus, in some populations, sedentary behavior may be more open to change compared to physical activity behavior. Interruptions in prolonged sedentary activities and replacing muscular inactivity with low-intensity activities (such as standing up instead of sitting) are easily accessible activities and they do not require much physical exertion of the individual. Therefore, it might be favorable to start with sedentary behavior change and gradually move on to physical activity behavior change.

SUMMARY

Among persons with OSAS and/or obesity, both an insufficient physical activity level and a high amount of sedentary time have been reported. The explanation for this is likely multifaceted, ranging from physical factors such as abnormal hemodynamic responses and higher oxygen requirement to cognitive aspects—for instance, feelings of not fitting in, and emotions such as fear of injury. Attending to an individual's prerequisites and strengthening self-efficacy, self-management, and self-regulation might encourage a behavior change in physical activity and sedentary time. Enhanced physical activity and reduced sedentary time have important implications for weight and body composition, but besides that, they contribute to several additional health benefits. Thus, these behaviors are most relevant to be addressed in health promotion for persons with OSAS and obesity.

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Chapter 33

Oxidative Stress in Sleep Apnea

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SLEEP APNEA SYNDROME

Sleep apnea syndrome (SAS) is a disease caused by sudden cessation from breathing during sleep and, thus, belongs to the group of so-called sleep-related breathing disorders. Apnea is technically defined as breathing cessation for more than 10 s. Using polysomnography SAS can be diagnosed if apneas are present more than 10 times during 1 h on average—the apnea index is higher than 10. Part of the polysomnography is also the continuous measurement of oxygen saturation. The oxygen desaturation index counts the number of desaturation episodes during 1 h. Last but not least, the respiratory disturbance index is used for the characterization of SAS patients (Jurkovicova & Celec, 2004). All the mentioned indices correlate with each other and although there are subtle differences, the informative value is very similar, with a great overlap. Some studies, however, show that oxygen desaturation index might be more specific and sensitive than the other indices (Chung et al., 2012).

SAS can be divided into three forms: central, obstructive, or mixed. The most common is the obstructive SAS, caused by narrowing of the upper airways due to an obstruction. The central form of SAS is rather rare, with a dysfunction of the cerebral respiratory regulation. Both forms of SAS can be distinguished with polysomnography. Muscular effort present during apneas is a sign of obstructive SAS. However, in many patients a mixed form of SAS, with a central and an obstructive component, is present (Abad & Guilleminault, 2004).

The cause of SAS in most cases is obesity, especially in the neck region, resulting in the obstruction of airways (Wolk, Shamsuzzaman, & Somers, 2003). However, obstructive SAS can also be caused by nasal polyps, hypertrophic tonsils, and a deviated nasal septum. Neurologic and cardiovascular, especially cerebrovascular, diseases that affect the medulla oblongata are the most common cause of central apneas (White, 2005). Although the etiology in a particular case seems to be clear, it has to be remembered that the association between SAS and obesity or cerebrovascular diseases is bidirectional. Both entities potentiate each other, making the diagnosis of SAS even more important for the clinical decisions.

Decades ago SAS was identified as a major risk factor for daytime sleepiness (Lavie, 1983). Interestingly, daytime sleepiness is more closely related to the number of apneas rather than to severity of oxygen desaturation (Johns, 1993). Untreated SAS increases the risk of motor vehicle crashes, resulting in high mortality of SAS patients (Ward et al., 2013). Excessive daytime sleepiness, however, also has other severe psychiatric complications, including reduced vigilance and higher risk of depression (Jacobsen, Shi, & Mokhlesi, 2013). Observational studies revealed that the major determinant of daytime sleepiness in SAS patients is the body mass index as a marker of obesity, with a close positive correlation (Chen et al., 2011). However, there seem to be other factors involved in this association beyond SAS, including endocrine, metabolic, and immune factors (Panossian & Veasey, 2012).

Taking back driving licenses from patients with SAS unfortunately does not prevent their higher mortality in comparison to the healthy population. SAS is associated with severe cardiovascular and metabolic complications. These include hypertension, both in the pulmonary and

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systemic circulation; ischemic heart disease; stroke; and diabetes mellitus (Harding, 2000). Of course, these complications are linked with each other and with their complications, such as cognitive decline, nephropathy, etc. The mechanisms behind the pathogenesis of SAS complications are not clear and are surely multifactorial. One of the major factors is the activation of the autonomous nervous system (Narkiewicz, van de Borne, Cooley, Dyken, & Somers, 1998). Sympathetic activation results in increased blood pressure and higher myocardial contractility. But it also affects other regulatory pathways, such as the renin–angiotensin–aldosterone system, glycemia control mechanisms, and inflammation (Di Murro et al., 2010; Ryan, Taylor, & McNicholas, 2009; Tahrani, Ali, & Stevens, 2013). The other major factor relating SAS to its complications is oxidative stress (Jurkovicova, Celec, Mucska, & Hodosy, 2003; Yamauchi & Kimura, 2008).

OXIDATIVE STRESS

Oxidative stress is defined as the disbalance between the production of free radicals and antioxidant mechanisms. This definition is of importance as it points towards two different causes leading to the same consequence. Overproduction of free radicals or insufficient antioxidant status both lead to oxidative stress (Valko et al., 2007). Free radicals are atoms or molecules with an unpaired electron that is causing their high reactivity. Depending on the particular atom with the unpaired electron, free radicals belong to reactive oxygen species (ROS) or reactive nitrogen species (RNS).

Both, ROS and RNS are produced under physiological conditions. They are involved in intracellular signaling pathways, mediate intercellular communication, and are involved in the detoxification of xenobiotics. They play a crucial role in inflammation. Superoxide anion radicals, nitric oxide, and hypochlorous acid are produced enzymatically to combat infections by nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, NO synthase, and myeloperoxidase (Sies & Degroot, 1992). However, the quantitatively largest production sites of ROS under physiological conditions are mitochondria. Terminal oxidation and respiratory complex produce, especially, superoxide in large amounts (Brand et al., 2004).

Aerobic metabolism is always associated with the production of ROS as byproducts of terminal oxidation. Aerobic organisms have, thus, mechanisms to cope with ROS. These include, especially, intracellular antioxidants such as superoxide dismutase and catalase (Chaudiere & Ferrari-Iliou, 1999). In addition, glutathione and its peroxidase–reductase system are important in scavenging ROS. Exogenous antioxidants such as ascorbic acid, tocopherol, and others contribute to the overall antioxidant status that prevents oxidative damage (Evans & Halliwell, 2001).

If the antioxidant mechanisms fail to scavenge all ROS, macromolecules such as lipids, nucleic acids, and proteins are at risk of being oxidized. This leads to disintegration of their structure, malfunctioning, and even changes in their epitopes and recognition by the immune system. Lipids are especially sensitive to oxidative damage. Numerous products of lipid peroxidation, especially malondialdehyde, can be measured to assess the severity of oxidative stress (Janero, 1990). Malondialdehyde, however, contains carbonyl moieties, which themselves are reactive, and thus, this product of oxidative damage contributes to the so-called carbonyl stress (Burcham & Kuhan, 1996).

One of the well-studied pathologies related to oxidative stress is the ischemia–reperfusion injury (Kaminski, Bonda, Korecki, & Musial, 2002). Whether it is the brain, heart, or kidney, the mechanism behind the injury is very similar. Ischemia is coupled with hypoxia or anoxia. Hypoxic cells can die or survive. The survival is dependent on the abilities of the cells to adapt to hypoxia via the action of hypoxia-inducible factor (HIF). One of the genes that are downregulated by HIF is superoxide dismutase. Superoxide dismutase is important for a cell during aerobic metabolism, which produces superoxide. During anoxia there is no oxygen and, thus, no aerobic metabolism and no superoxide. Production of such a large enzyme does not make sense for a hypoxic cell. When reperfusion is induced—in an experiment or in the clinic—the blood oxygen turns on the aerobic metabolism, leading to standard production of ROS that cannot be scavenged anymore (Dhalla, Elmoselhi, Hata, & Makino, 2000). The adaptation to hypoxia is thus paradoxically causing the subsequent damage during the reperfusion period, leading to apoptosis or necrosis. This ischemia–reperfusion injury is similar to the intermittent hypoxia in SAS (Jurkovicova et al., 2003).

Numerous biomarkers of oxidative damage are used. The most common are malondialdehyde as a marker of lipid peroxidation (Janero, 1990), protein carbonyls, and advanced oxidation protein products as markers of protein oxidation (Cho, Roman, Yeboah, & Konishi, 2007) and hydroxydeoxyguanosine as a marker of oxidative damage to DNA (Helbock, Beckman, & Ames, 1999). The choice of markers depends on the disease entity, the tissue or liquid sample being used, and, of course, the research question. The most sensitive, although rather unspecific, are the so-called thiobarbituric acid reacting substances (TBARS), which include the aforementioned malondialdehyde but cover other molecules—lipid peroxidation products that complicate specific malondialdehyde measurement (Dillard & Tappel, 1989). TBARS were measured often in patients with SAS.

SAS AND OXIDATIVE STRESS

SAS has several cardiovascular complications, including hypertension, atherosclerosis, and ischemic heart diseases (Bradley & Floras, 2009; Leung & Bradley, 2001). They all are linked, and from a pathophysiological view

they represent a single entity with various stages and phenotypes. One common important factor in the pathophysiology of these disorders is oxidative stress. Overproduction of superoxide and other ROS leads to reactions with nitric oxide and the production of peroxynitrite (Radi, 2013). Peroxynitrite is even more reactive than the substrates, and in addition, the reaction leads to lack of nitric oxide. As nitric oxide is an important vasodilator, long-term oxidative stress leads to vasoconstriction and increased blood pressure (Hoeldtke, Bryner, McNeill, Hobbs, & Baylis, 2003).

Another pathway is carbonyl stress. As mentioned above, lipids are the most sensitive macromolecules when it comes to oxidative damage. The main product of lipid peroxidation is malondialdehyde, and this is a carbonyl compound. Carbonyls interact with free amino groups on proteins, nucleic acids, and other molecules (Cline, Riggins, Tornaletti, Marnett, & Hanawalt, 2004; Lecomte et al., 1993; Li, Li, Sheng, & Yin, 2005). Similarly to oxidative damage, carbonylation leads to changes in the structure and loss of function. Malondialdehyde and its protein adducts are increased in patients with SAS, showing that lipid peroxidation is increased in SAS (Jurado-Gamez et al., 2012). Carbonyl stress can thus cause endothelial dysfunction, leading once more to increased blood pressure and to a higher risk of atherosclerosis.

Carbonyl stress is important in the pathogenesis of diabetic complications. The inductor is not malondialdehyde in this case, but the open form of glucose, which is increased in untreated diabetic patients (Turk, 2010). Chronic hyperglycemia leads to glycation of protein and nucleic acids in a reaction called the Maillard reaction (Thorpe & Baynes, 1996). Maillard reaction products are researched in food chemistry as well as in diabetology. The final group of heterogeneous compounds that is produced during carbonyl stress is called advanced glycation end-products (AGEs). AGEs are more than just a simple marker of carbonyl stress. They are recognized by the receptor for AGEs (RAGE) and RAGE activation leads to inflammation that further increases the production of ROS (Yan, Ramasamy, & Schmidt, 2008).

Research on atherosclerotic plaques revealed that although low-density lipoprotein (LDL) cholesterol is no doubt a risk factor for atherosclerosis, the foam cells in the plaques do not contain LDL but oxidized LDL particles (Klinkner, Waites, Kerns, & Bugelski, 1995). This is of importance, because it explains why some patients have high LDL cholesterol without atherosclerosis. What really increases the risk of atherosclerosis is the co-occurrence of high LDL cholesterol and oxidative stress. Oxidized LD particles are recognized and phagocytized, but cannot be metabolized, by monocytes/macrophages. Foam cells are formed—the basis of the atherosclerotic plaque (Gerrity, 1981). SAS patients suffer from an increased risk of atherosclerosis (Weinreich et al., 2013).

All of the abovementioned mechanisms are relevant if SAS is associated with oxidative stress. And it is. Although there surely are alternative explanations, the most probable source of ROS in SAS is the hypoxia–reoxygenation injury (Jurkovicova et al., 2003). Apneas lead to oxygen desaturation and, thus, to limited tissue hypoxia. After apnea ends, oxygen saturation increases and tissue hypoxia disappears. And this repeats, apnea after apnea, 20–30 times in an hour during sleep every night in patients with SAS. The previously published hypothesis postulated that chronic intermittent hypoxia in SAS patients resembles chronic intermittent ischemia–reperfusion of the heart, kidney, and other organs (Jurkovicova et al., 2003). It is probably similar to the microenvironment in a fast-growing tumor. The adaptation of cells to hypoxia is a general phenomenon that is present in most types of cells. Thus, in the endothelium of vessels in SAS patients the same mechanisms are ongoing, like in the myocardium after reperfusion. Adaptation to low oxygen includes the decrease in antioxidant enzymes and increase in the production of angiogenic molecules. During the arousal apnea is compensated by hyperventilation that makes the reoxygenation phase even faster and potentially more dangerous.

CLINICAL STUDIES ON OXIDATIVE STRESS IN SAS

Numerous clinical studies have shown that SAS is associated with oxidative stress. The studies were mostly comparisons between SAS patients and controls. Differences were in the markers measured and in the detailed characteristics of the patients, especially the severity of SAS. Of course, the sample size varied considerably between studies. Already at the beginning of the research focusing on oxidative stress in SAS, it was known that patients with SAS have a lower antioxidant capacity (Christou, Moulas, Pastaka, & Gourgoulianis, 2003) but also higher amounts of ROS (Christou, Markoulis, Moulas, Pastaka, & Gourgoulianis, 2003). Later it was found that untreated SAS patients suffer from low ferric reducing ability of plasma (Mancuso et al., 2012), low paraoxonase (Baysal et al., 2012), and low superoxide dismutase activity (Sales et al., 2013). The low antioxidant capacity might be the primary cause, but also a secondary consequence, of long status of overproduction of ROS. Usually, there is a negative correlation between oxidative damage markers and antioxidant status. This is similar in SAS patients (Wysocka et al., 2008). The correlation is dependent on the stage and severity of SAS (Cofta et al., 2008). In an interesting study measuring 8-isoprostane in blood and in the exhaled breath, it was shown that SAS patients suffer from both systemic and local oxidative stress (Carpagnano et al., 2002). As lipids are most susceptible to oxidative damage, it is not surprising that lipid peroxidation marker—malondialdehyde—is higher in

patients with SAS (Dikmenoglu et al., 2006; Ozturk et al., 2003; Wang, Li, Xie, & Zhang, 2010). Its concentrations are linked with the increase in cellular adhesion molecules (Jurado-Gamez et al., 2012). Isoprostanes are also markers of lipid peroxidation and are similarly higher in patients with SAS (Monneret et al., 2010). Proteins are less susceptible to oxidative damage. Advanced-oxidation protein products are higher in SAS patients versus controls, but the difference was not statistically significant (Sonka et al., 2008). Interestingly, the concentrations correlate with the apnea index. When protein carbonyls were measured, the concentrations were higher in SAS patients in comparison to controls, similar to malondialdehyde (Vatansever, Surmen-Gur, Ursavas, & Karadag, 2011).

Only a few studies are published that showed no differences in oxidative stress between patients and controls (Grabska-Kobylecka et al., 2008; Kang, Jung, & Kim, 2013). In some studies a number of markers were measured but only a few were different in comparison to controls (Ntalapascha et al., 2013). Whether this is the result of publication bias is not clear. But obesity present in most cases of SAS is also associated with oxidative stress (Lee, Ju, Choi, Kim, & Yoon, 2012). This has to be taken into account when analyzing the relationship of SAS and oxidative stress. Multifactorial analysis including several factors known for affecting oxidative stress showed that SAS does have to be an independent determinant of oxidative stress (Simiakakis et al., 2012).

In SAS patients, similar to diabetic patients, carbonyl stress markers—AGEs—are higher than in a healthy population (Tan et al., 2006). One of the specific AGE compounds, however, was comparable between patients and controls (Tokuda, Sando, Matsui, & Yokoyama, 2009). In this aspect, it should be noted that in severe SAS, concentrations of the soluble receptor for AGEs—the "scavenger" of AGEs—are low (Volna et al., 2011). Oxidative and carbonyl stress affects DNA directly and indirectly. Telomeres are shorter in leukocytes from SAS patients (Barcelo et al., 2010). And the increased turnover of cells leads to increased concentrations of cell-free extracellular DNA (Shin et al., 2008). Levels of copper and iron, which can induce free radical production via the Fenton reaction, are higher in patients with SAS (Chen, Guo, Tseng, Wang, & Liu, 2013).

THE EFFECTS OF CONTINUOUS POSITIVE AIRWAY PRESSURE ON OXIDATIVE STRESS

The current gold standard of treatment of SAS is continuous positive airway pressure (CPAP). It has been repeatedly shown that CPAP reduces the cardiovascular risk of SAS patients (Kaneko et al., 2003; Marin, Carrizo, Vicente, & Agusti, 2005). One of the first studies analyzing the effects of CPAP on oxidative stress showed that neutrophils producing superoxide became less active after CPAP therapy (Schulz et al., 2000). Even a single night with CPAP is enough to decrease oxidative stress in SAS patients (Christou et al., 2009). CPAP decreased the concentration of 8-isoprostane as a marker of local respiratory oxidative stress and increased nitric oxide in exhaled breath (Carpagnano et al., 2003; Chua et al., 2013). CPAP also decreased lipid peroxidation after 3 and 6 months (Oyama et al., 2012; Yagihara et al., 2012), but also after a single night (Alzoghaibi & Bahammam, 2012). For the clinical use of such measurements, it is important that some of the markers of oxidative and carbonyl stress can be measured in saliva instead of plasma and the salivary concentrations have similar dynamics after CPAP (Celec et al., 2012). However, one night with CPAP does not alter salivary oxidative stress markers (Tothova, Hodosy, Mucska, & Celec, in press). Thioredoxin in plasma is higher in patients with SAS, but when treated with CPAP the concentrations of thioredoxin decrease (Takahashi et al., 2008). Thioredoxin might be even more interesting, as its concentrations correlate with SAS severity (Guo, Wang, Li, Li, & Wan, 2013). Subtle but significant reduction of oxidative stress in SAS can be achieved with other treatments, such as the Herbst mandibular advancement splint (Itzhaki et al., 2007). However, the effect sizes are much smaller than with CPAP. Overproduction of free radicals, especially superoxide, leads to a depletion of bioavailable nitric oxide. In patients with SAS decreased levels of nitric oxide were found, suggesting a mechanism for the endothelial dysfunction (Kohler & Stradling, 2010; Ozkan, Firat, Simsek, Torun, & Yardim-Akaydin, 2008) but also for cognitive symptoms such as depression and anxiety (Franco et al., 2012). This can be reversed by the CPAP treatment (Jelic et al., 2008). CPAP also has positive metabolic effects, especially on insulin sensitivity. This effect is related to reduction of lipid peroxidation (Dorkova, Petrasova, Molcanyiova, Popovnakova, & Tkacova, 2008). The effects on hypertension seem to be clearer than on insulin resistance (Murri et al., 2009), but this varies from study to study (de Lima et al., 2010). Antioxidative status that is low in patients with severe SAS is not affected by CPAP (Katsoulis et al., 2011).

If oxidative stress plays a crucial role in the pathogenesis of SAS-related cardiovascular complications, then carefully chosen antioxidants might have beneficial effects even without CPAP treatment. And indeed, in animal models of SAS antioxidant treatment decreases blood pressure (Troncoso Brindeiro, da Silva, Allahdadi, Youngblood, & Kanagy, 2007). In humans antioxidants improved the endothelial function (Buchner et al., 2011). In our experiment vitamins C and E in combination decreased oxidative and carbonyl stress (Celec et al., 2013). It is very likely that the combination of water-soluble and oil-soluble antioxidant was the basis of the positive results.

CONCLUSION

SAS is associated with oxidative stress, which is the underlying mechanism of vascular dysfunction, hypertension, atherosclerosis, and ischemic heart disease. CPAP treatment decreases oxidative and carbonyl stress. But for some patients that are nonadherent to CPAP, there is a need for an alternative. Antioxidant treatment seems to be a rational choice. However, there are very few studies analyzing the effects of antioxidants in SAS. In addition, there is a need for more data from animal models. Novel antioxidants and novel approaches to antioxidant therapy, especially combinations of antioxidants, antioxidant gene therapy, and potentially also antioxidant-producing recombinant probiotics, might represent a future alternative and may be an additional treatment for patients with SAS.

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Part VII

Alcohol and Sleep Dysfunction

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Chapter 34

Sleep in Fetal Alcohol Spectrum Disorders

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INTRODUCTION

Fetal alcohol spectrum disorders (FASD) comprise a group of conditions characterized by lifelong neurodevelopmental disabilities arising from maternal consumption of alcohol during pregnancy, or prenatal alcohol exposure (PAE) (Bertrand, Floyd, Weber, et al., 2004; Olson, Ohlemiller, et al., 2009; Stratton, Howe, & Battaglia, 1996). The prevalence of the full range of FASD has been estimated as high as 9–10 cases per 1000 live births in the United States (May & Gossage, 2001; Sampson et al., 1997), and more recently through in-school studies as high as 2–5% of younger school children in the United States (May et al., 2009). FASD is considered a major public health problem (Riley & McGee, 2005; Warren et al., 2005) that is global in extent (Calhoun et al., 2006; May et al., 2009; Warren et al., 2005). FASD is known to have frequent, serious sequelae, including multiple secondary disabilities in lifestyle and daily function (Streissguth et al., 2004), adverse impact on caregiver and family function (Olson, Oti, Gelo, & Beck, 2009), and high societal costs (Lupton, Burd, & Harwood, 2004; Riley & McGee, 2005). This makes it essential to understand all facets of this clinical condition, especially those with diagnostic and treatment implications.

CHARACTERIZING SLEEP PROBLEMS IN CHILDREN WITH FETAL ALCOHOL SPECTRUM DISORDERS

Several early research groups generally identified sleep problems among individuals with FASD. An early longitudinal study in Germany examined a clinical sample of individuals with FASD ($N=158$) at three time points: preschool, school-age, and adolescence (Steinhausen & Spohr, 1998). Using questionnaires and clinical interviews, "sleep disorders" were noted as a common problem. Importantly, many participants showed newly manifested sleep disorders at the school-age time point. No details were given about types and exact frequency of sleep disorders, nor were validated measures used. A U.S. study ($N=472$) found that just over 50% of informants identified "sleeping problems" (Streissguth, Bookstein, Barr, Press, & Sampson, 1998). A U.S. chart review ($N=2231$) of youth referred for FASD diagnosis found "sleep disorder" rates of 9.7% (no prenatal alcohol exposure) to 52.3% (high-risk alcohol exposure) (Bhatara, Loudenberg, & Ellis, 2006). A recent survey of children with FASD in Canada ($N=89$), aged 8–15 years, found 62% with "sleeping disorders" gathered from clinical interview compared to 11% of controls (Green et al., 2009). This was the most prevalent comorbidity, occurring at a similar rate to attention deficit hyperactivity disorder (ADHD)/attention deficit disorder. These studies, which were not designed to specifically assess for sleep problems, served to establish that "sleep problems," however vaguely characterized, are prevalent among those with FASD.

Research focusing on sleep difficulties in children with FASD continues to emerge. Unpublished cross-sectional findings from children with FASD ($N=100$), aged 5–8 years, used sleep diaries and an unnamed, apparently validated caregiver questionnaire on child sleep. Findings included reduced sleep duration and reports that 55%

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of the sample had >2 night wakings (Stade et al., 2008). Subsequently, other studies have uniformly revealed a very high rate of clinically significant sleep problems in several samples of children with FASD, also suggesting that primary difficulties with sleep initiation and maintenance were common (Chen, Olson, & Astley, 2006; Chen, Olson, Picciano, Starr, & Owens, 2012; Wengel, Hanlon-Dearman, & Fjeldsted, 2011). Chen et al. performed a detailed study comparing the validated Children's Sleep Habits Questionnaire (CSHQ) (Owens, Spirito, & McGuinn, 2000) Total Score and subscores from a representative subset of children with FASD and concerning daytime behaviors ($n=33$), aged 4–10 years, and data from an age-matched typically developing community sample ($N=418$). Overall, a striking 85% ($n=28$) fell above the cutoff for clinically significant sleep problems (CSHQ Total Score ≥41), significantly more than the 35% ($n=146$) seen in controls ($p<0.001$). In addition, subscales concerning pediatric insomnia were also elevated in children with FASD compared to controls. Wengel et al. found remarkably similar CSHQ scores and differences between a group of younger children (ages 3–6 years) with FASD compared to controls (Wengel et al., 2011). Chen et al. also performed a full overnight sleep study for five of these children with FASD, all of whom had CSHQ scores >41 (Chen et al., 2012). Polysomnography showed objective evidence of fragmented sleep among children with FASD, as well as mildly elevated carbon dioxide levels suggesting sleep-disordered breathing (SDB). CSHQ data were available for six of the children with FASD; all six received total scores ≥41 (range: 46–72). No clear association was found between the CSHQ Total Score and degree of sleep fragmentation or SDB. Findings from these pilot polysomnography data coupled with CSHQ data from both studies suggest that two broad areas where children with FASD may have concentrated sleep difficulties are difficulties with sleep initiation/maintenance and respiratory disturbances.

CHARACTERIZING SLEEP DISRUPTION IN MODELS OF PRENATAL ALCOHOL EXPOSURE

Not every child with PAE will go on to have FASD, and the progression of this is dependent on a multitude of factors well outside the scope of this chapter. As the literature reveals, children with FASD, which is typically not diagnosed until preschool or school age, may suffer from sleep difficulties related to in utero exposures worsened by postbirth events. Thus, investigating the connection between primary PAE (as opposed to children clinically diagnosed with FASD) and sleep disruption starts to address possible mechanistic relationships between the two. Illustrative examples of altered sleep architecture, fragmentation, and shorter sleep duration are evident from two bodies of literature. First, there are correlational data from studies of infants and older children with history of PAE, who may or may not fulfill criteria later in life of FASD. Early infant studies in North America, using electroencephalography, with prenatal alcohol exposure assessed both prospectively in pregnancy and retrospectively, showed adverse changes in state regulation including sleep (Rosett et al., 1979) and in sleep cycling and arousal (Chernick, Childiaeva, & Ioffe, 1983; Havlicek, Childiaeva, & Chernick, 1977; Ioffe & Chernick, 1988; Loffe, Childiaeva, & Chernick, 1984; Scher, Richardson, Coble, Day, & Stoffer, 1988). This was true even though these children were not experiencing acute withdrawal. Research again took up this intriguing topic, finding that alcohol-exposed infants may have altered arousal responses during sleep (Troese et al., 2008). Subsequently, a longitudinal study in Finland has extended the study of sleep and prenatal alcohol exposure into childhood. Associations between low birth weight, prenatal exposure to alcohol and tobacco, and sleep duration and efficiency (based on actigraphy, or measurement of sleep movement) were examined in 8-year-olds ($N=289$). Prenatal alcohol exposure was associated with shorter sleep duration and poorer efficiency, even after controlling for birth weight and tobacco exposure. No assessments of daytime function or FASD diagnosis were undertaken (Pesonen et al., 2009).

Second, there are data from experimental animal models of prenatal alcohol exposure, primarily using rats, which demonstrate possible mechanisms. These suggest that sleep compromise starts early in life and persists across the lifespan. In alcohol-exposed rat pups compared to controls, disturbances in sleep–wake patterns were found (Hilakivi, 1986; Hilakivi et al., 1987). Further studies have shown altered circadian functioning (Allen, West, Chen, & Earnest, 2005; Fukui & Sakata-Haga, 2009; Sakata-Haga et al., 2006) with genetic molecular correlates (Farnell et al., 2008) that may predispose exposed individuals to nocturnal sleep fragmentation. Early data reveal blunted ventilatory responses to hypoxia in juvenile rats with prenatal alcohol exposure (Dubois, Houchi, Naassila, Daoust, & Pierrefiche, 2008; Dubois, Kervern, Naassila, & Pierrefiche, 2013; Kervern, Dubois, Naassila, Daoust, & Pierrefiche, 2009). These data suggest that increased risk for significant SDB could occur. Importantly, selective sleep deficits were found in young adult rats with concurrent deficits in spatial memory, which persisted but could be attenuated with treatment (Stone et al., 1996). Both these human and animal data correlate to what is clinically seen in school-aged children with FASD in the limited number of studies done to date.

MECHANISTIC LINKS BETWEEN PRENATAL ALCOHOL EXPOSURE AND SLEEP DIFFICULTIES

There are physiological reasons why children with FASD may be predisposed to sleep fragmentation and SDB. First, animal models and neuroimaging studies reveal

that prenatal alcohol exposure affects development of the cerebellar vermis in utero (Dikranian, Qin, Labruyere, Nemmers, & Olney, 2005; Riley & McGee, 2005; Spadoni, McGee, Fryer, & Riley, 2007), an area presumed to play a role in central respiratory control and respiratory muscle coordination (Verrier, Harper, & Hobson, 2005). Cerebellar anomalies are found in individuals across the spectrum of FASD (Rasmussen, Horne, & Witol, 2006). Other research offers relevant data through examining children with lesions in the cerebellar vermis, who show a markedly higher incidence of apneas (Chen et al., 2005). Second, SDB could be present due to low neuromotor tone and craniofacial abnormalities, as seen in midfacial hypoplasia in other conditions (predisposing to inefficient ventilatory muscle excursion and upper airway collapse) (Wills, Swift, & Moller, 2006), and is also known to exist at least in those with full FAS (Chudley et al., 2005; Riley & McGee, 2005; Stratton et al., 1996). These two lines of thinking suggest the possibility that those with FASD experience respiratory abnormalities during sleep arising from cerebellar abnormalities and/or upper airway obstruction. Third, neuroimaging and animal research suggests children with FASD may also be predisposed to teratogenic damage to the suprachiasmatic nucleus, presumed to play a critical role in the circadian clock (Earnest, Chen, & West, 2001). PAE in mice has also been shown to decrease levels of γ-aminobutyric acid (GABA), an important neurotransmitter in sleep–wake stability (Godin, Dehart, Parnell, O'Leary-Moore, & Sulik, 2011). A dysfunctional circadian system and/or disrupted GABA circuits may lead to frequent night arousals (clinical and subclinical) and, further, to insomnia, perhaps because awake and sleep states are not appropriately recognized at a neurological level. Respiratory abnormalities, from central nervous system (CNS) impairment and/or SDB, may also result in repeated cortical arousals during sleep, again leading to sleep fragmentation (Katz & Marcus, 2005). If these insults are combined, sleep can be further fragmented through arousals.

SLEEP PROBLEMS AND PSYCHOSOCIAL RISK

As mentioned earlier, not every child with PAE meets diagnostic criteria for FASD in later childhood, and it stands to reason that extra-utero environmental modifications of risk for development of sleep disruptions likely occur. This becomes notable due to the high rates of negative or unpredictable caregiving environments in childhood for those with FASD (Olson, Jirikowic, Kartin, & Astley, 2007). Children's cultural/racial background and psychosocial risk have been associated with differences in sleep patterns and parental sleep expectations (Jenni & O'Connor, 2005). Proximal measures of risk, such as chaotic living conditions, are salient to sleep problems (Brown & Low, 2008). Socioeconomic status (SES) may moderate the impact of sleep disruption on daytime functioning, with those experiencing higher SES somewhat protected from negative impact and those with lower SES more affected (Buckhalt, El-Sheikh, & Keller, 2007; El-Sheikh, Buckhalt, Keller, Cummings, & Acebo, 2007; Moore, Adler, Williams, & Jackson, 2002).

IMPACT OF SLEEP DIFFICULTIES ON DAYTIME FUNCTION

Growing data associating difficulties in sleep and daytime function suggest that, overall, disrupted childhood sleep is associated with increased incidence of problems in child health and quality of life and deficits in emotional, behavioral, cognitive, and academic function. This is found in typical and atypical populations worldwide. For example, in typically developing school-aged children ($N=135$), fragmented sleep assessed with actigraphy showed that poor sleepers had lower performance on a complex working memory task and a continuous performance sustained attention task, and elevated Child Behavior Checklist (CBCL) ratings (total problems, thought disorder, delinquent behavior) (Sadeh, Gruber, & Raviv, 2002). Children, aged 4–9 years ($N=1391$) with current sleep problems also had multiple elevated CBCL scores (Shang, Gau, & Soong, 2006). Associations between sleep and daytime function are seen in pediatric clinical populations. In a sample of children with ADHD ($N=239$), aged 5–18 years, an association was found between sleep problems and lower child quality of life (using the PedsQL 4.0), and with number of days missed or late to school, with or without covarying severity of ADHD symptoms (Sung, Hiscock, Sciberras, & Efron, 2008). In autism spectrum disorders, parent report revealed an association between ratings of poor sleep and less optimal child daytime behavior on the CBCL. There were also moderate associations between sleep latency from polysomnography and CBCL ratings (especially affective problems and aggressive behavior) (Malow et al., 2006). Interestingly, sleep problems are related to problems on many scales that are also the most elevated in studies of children with FASD (Astley et al., 2009; Mattson & Riley, 2000).

Data on restricted sleep and SDB (which encompasses problems of obstructive sleep apnea) shed further light on the connection between sleep and daytime function, at school and at home. For example, in a within-subjects design, teachers rated children with restricted sleep as having greater attention problems, more sleepiness, and increased academic problems, compared to optimized sleep (≥10 h in bed) (Fallone, Acebo, Seifer, & Carskadon, 2005). Sleep restriction data suggest a causal association. There is evidence that obstructive sleep apnea, currently the best-studied model of sleep fragmentation in children, is associated with poor school performance, neurocognitive deficits, daytime hyperactivity,

behavior problems, mood instability, and decreased growth in general pediatrics (Chervin & Archbold, 2001; Rosen, Palermo, Larkin, & Redline, 2002). These are all common and problematic symptoms in FASD (Astley et al., 2009; Bertrand et al., 2004; Mattson & Riley, 2000; O'Connor & Paley, 2009; Riley & McGee, 2005; Stratton et al., 1996). Pediatric studies have found that SDB is associated with deficits in behavior and emotion regulation, scholastic performance, sustained attention, selective attention, and alertness (Beebe, 2006; Gottlieb et al., 2003) and with lower scores on measures of phonological processing, executive functioning, and visual attention (O'Brien et al., 2004). Surgical treatment in children with SDB leads to improved sleep and daytime function, again suggesting a causal connection (Chervin et al., 2006). Treatment of SDB leads to notable decreases in health-care utilization and likely improves child quality of life. Sleep problem diagnosis and treatment seem to have potential to improve daytime function and reduce health-care costs (Reuveni, Simon, Tal, Elhayany, & Tarasiuk, 2002; Tarasiuk, Simon, Tal, & Reuveni, 2004).

Many studies have documented the type and extent of dysfunction in daytime learning and behavior among children with FASD. But none, to our knowledge, have examined difficulties in daytime function in relation to sleep problems. This is surprising, because sleep fragmentation from various causes has been linked to deficits in attention, response inhibition, and working memory (Anderson, Storfer-Isser, Taylor, Rosen, & Redline, 2009; Dahl, 1996; Gozal & Kheirandish-Gozal, 2007; Sadeh, 2007). These are all areas of neuropsychological impairment well documented among children with FASD (Kodituwakku, 2009). At our institution, among the 34 children with FASD who completed the CSHQ as reported by Chen et al., exploratory findings revealed daytime behavioral deficits, especially problems in inhibition and working memory, using the Behavior Rating Inventory of Executive Function (BRIEF) questionnaire (Gioia, IIsquith, Guy, & Kenworthy, 2000), a parent questionnaire designed to assess day-to-day child behaviors reflecting executive function dimensions: behavioral regulation and meta-cognition. The BRIEF has high internal consistency and test–retest reliability, has been used to profile FASD samples (Rasmussen et al., 2006), and is sensitive to sleep disturbance (Anderson et al., 2009). BRIEF scales assessing these two domains, and the composite score, were significantly correlated with sleep problems assessed by the CSHQ Total Score (see Table 1). Children with more severe sleep complaints tended to have more executive function impairment.

TABLE 1 Correlations of Behavior Rating Inventory of Executive Function (BRIEF) and Children's Sleep Habits Questionnaire (CSHQ) Scores in Children with Fetal Alcohol Spectrum Disorders

BRIEF Domain/ Composite	BRIEF T-score	Correlation: CSHQ Total Score	*p* Value
Inhibition	74.9 ± 10.4	0.42	0.013
Working memory	75.2 ± 10.6	0.42	0.014
Global executive composite	76.6 ± 11.5	0.57	<0.001

IMPACT OF SLEEP DIFFICULTIES ON CAREGIVER FUNCTION

Child sleep disruption is increasingly understood to increase caregiver burden and negatively impact parents' sleep, in typical (Meltzer & Mindell, 2007; White, White, & Fox, 2009) and atypical populations (Doo & Wing, 2006; Hoffman et al., 2008; Meltzer & Mindell, 2006; Sung et al., 2008). Treatment helps, as studies of sleep interventions used with younger children show improved caregiver sleep, mood, and marital satisfaction after treatment (Mindell & Durand, 1993). There are very high levels of stress and psychological distress among parents of children with FASD (Olson, Oti, et al., 2009), which appear directly related to the child's functional impairments (Paley, O'Connor, Frankel, & Marquardt, 2006). Sleep problems are an important area of functional impairment in FASD, and comprise an intervention target with potential to improve the lives of both parents and children.

CONCLUSION

At a very fundamental level, adequate and good-quality sleep is a cornerstone to maximizing a child's neurodevelopmental potential and overall well-being. Children with FASD, who already show evidence of CNS dysfunction, do not have good sleep. Children with FASD suffer from high rates of sleep difficulties, preliminary characterizations of which include difficulties with sleep fragmentation and respiratory disturbances. Several studies of human infants and animal models have illustrated these clinical findings. Mechanistically, several plausible pathways exist linking PAE to sleep difficulties and subsequent daytime dysfunction. Postnatal stressors, including high psychosocial risk and parental stress within affected families, must also be considered and addressed. Ultimately, identification and treatment of sleep disorders in children with FASD is an intervention target with high utility, given the possibility to improve their functional outcomes, overall health, and both child and family quality of life (Jan et al., 2010).

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Chapter 35

Adenosine and Glutamate in Neuroglial Interaction: Implications for Sleep Disorders and Alcoholism

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INTRODUCTION

Adenosine is a nucleoside with functions that are crucial to proper brain function (Burnstock, 2006, 2008; Latini & Pedata, 2001). As the product of ATP hydrolysis, adenosine serves as an indicator of metabolic activity (Dunwiddie & Masino, 2001). The physiological effects of adenosine are directly related to its metabolic function. For example, adenosine dilates blood vessels in the brain, thereby coupling the energy demands of neurons with blood flow necessary to maintain their activity. In addition, adenosine takes on a related role as a modulator of neurotransmission. This role appears particularly important in the fine-tuning of excitatory glutamatergic signaling (Figure 1; Ruby, Adams, Knight, Nam, & Choi, 2010).

Extracellular adenosine, normally ranging from 25 to 250 nM concentration, is highly regulated by production and transport (Burnstock, 2006, 2008; Parkinson, Ferguson, Zamzow, & Xiong, 2006). Thus, adenosine levels can change rapidly to fine-tune the activity of neighboring neurons. Adenosine reaches extracellular space via two mechanisms: (1) it is produced extracellularly from ATP released by neurons or astrocytes, and (2) it is released by neurons (Lovatt et al., 2012; Wall & Dale, 2013) or astrocytes (Parkinson et al., 2006) via equilibrative nucleoside transporters (ENTs). Mounting evidence suggests that many of the known roles of adenosine are a result of neuroglial interactions (Araque, Parpura, Sanzgiri, & Haydon, 1999; Halassa, Florian, et al., 2009; Pascual et al., 2005).

Adenosine reduces neuronal excitability through four subtypes of G protein-coupled receptors, A1R, A2AR, A2BR, and A3R, each with a distinct affinity for adenosine (Fredholm, 2010). The A1R and A2AR have relatively high binding affinity (10–100 nM) and are activated at physiological levels of adenosine. A1R are Gi coupled, are expressed ubiquitously, and inhibit neuronal activity and glutamate release (Halassa, Florian, et al., 2009). A2AR are Gs coupled, increasing cyclic adenosine 3′,5′ monophosphate (cAMP) production. Although A2AR are excitatory at the cellular level, they are expressed in the striatopallidal circuit, inhibiting motor activity (Aoyama, Kase, & Borrelli, 2000). A2AR also associate physically with A1R, dopamine D2R, and glutamate mGluR5 receptors (Ciruela et al., 2006; Ferre et al., 2010).

Adenosine has well-established roles in homeostatic sleep and alcohol use disorders (Asatryan et al., 2011; Cunha, Ferre, Vaugeois, & Chen, 2008; Nam et al., 2012; Ruby et al., 2010). While adenosine itself mediates sleep, adenosinergic fine-tuning of glutamate signaling controls circadian timing and alcohol-related behavior. Dysregulated striatal adenosine-modulated glutamate transmission contributes to the effects of, and abuse potential for, alcohol (Chen et al., 2010; Choi et al., 2004; Nam, Lee, Hinton, & Choi, 2010).

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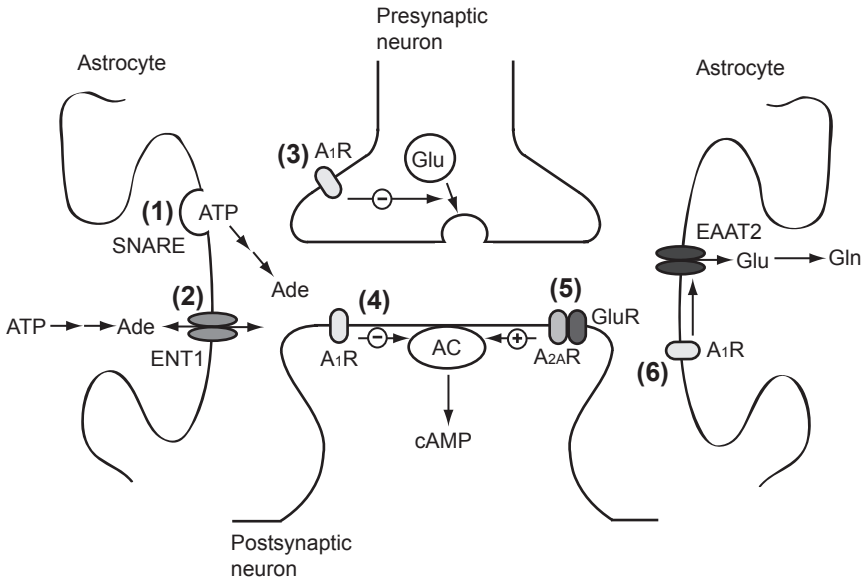

FIGURE 1 Schematic representation of neuroglial adenosine-mediated fine-tuning of glutamatergic neurotransmission. (1) SNARE-mediated ATP release by astrocytes provides a major source of adenosine (Ade) in extracellular space. (2) Adenosine levels are also highly regulated by ethanol-sensitive equilibrative nucleoside transporter 1 (ENT1), a bidirectional nucleoside transporter. (3) Activation of presynaptic A1 receptors (A1R) inhibits glutamate (Glu) release. (4) Activation of postsynaptic A1R inhibits adenylate cyclase (AC) to reduce production of cyclic adenosine monophosphate (cAMP). (5) Activation of Gs-coupled A2A receptors (A2AR) stimulates the production of cAMP by AC. (6) A1R activation on astrocytes regulates the expression of excitatory amino acid transporter 2 (EAAT2), which is responsible for the majority of glutamate uptake in the central nervous system. Gln, glutamine.

Recent studies elucidating neuroglial mechanisms of adenosine signaling may lead to new therapeutic opportunities for the treatment of sleep, circadian, and alcohol use disorders.

PURINERGIC REGULATION OF HOMEOSTATIC SLEEP BY ASTROCYTES

Adenosine accumulates with wakefulness and promotes sleep by activating A1R, which inhibits the wake-promoting neurons of the basal forebrain (BF) (Basheer, Strecker, Thakkar, & McCarley, 2004; Porkka-Heiskanen et al., 1997; Radulovacki, Virus, Djuricic-Nedelson, & Green, 1984; Thakkar, Winston, & McCarley, 2003), driving sleep pressure and intensity as a function of prior time awake (Brown, Basheer, McKenna, Strecker, & McCarley, 2012; Schmitt, Sims, Dale, & Haydon, 2012). Sleepiness is mimicked by systemic or central administration of adenosine or A1R agonists (Basheer et al., 2004; Blutstein & Haydon, 2013; Frank, 2013). During sleep deprivation, extracellular adenosine and A1R expression increase (Basheer et al., 2004; Brown et al., 2012), initiating rebound sleep. Mice in which soluble N-ethyl maleimide-sensitive fusion protein attachment protein receptor (SNARE)-mediated gliotransmission is attenuated (dnSNARE) exhibit decreased rebound sleep that is mimicked by A1R antagonism, suggesting that purinergic gliotransmission regulates sleep homeostasis (Halassa, Fellin, & Haydon, 2009). As dnSNARE mice have normal baseline sleep, release of adenosine via ENTs may be important for basal sleep pressure.

Astrocytes promote wakefulness by clearing adenosine during sleep via ENTs facilitating adenosine influx, and adenosine kinase (AK), which phosphorylates intracellular adenosine to AMP. Astrocytic AK downregulation increases inhibitory transmission, whereas overexpression of AK has the opposite effect (Diogenes et al., 2014), accelerating adenosine clearance and diminishing rebound sleep (Dias, Rombo, Ribeiro, Henley, & Sebastiao, 2013). The second pathway for adenosine clearance is extracellular breakdown to inosine by adenosine deaminase (AD). A genetic variant of human AD reduces adenosine breakdown, which heightens sleep pressure, waking alpha wave activity, and fatigue (Bachmann et al., 2012). Although much remains to be discovered, neuroglial mechanisms are clearly indispensable to sleep homeostasis.

ADENOSINERGIC MODULATION OF CIRCADIAN RHYTHMS

Circadian rhythms are regulated by the suprachiasmatic nucleus (SCN), a biological clock whose timing is reset by photic (light) input and nonphotic (behavioral) input. A1R activation attenuates photic phase resetting by inhibiting glutamate release in the SCN (Hallworth, Cato, Colbert, & Rea, 2002; Sigworth & Rea, 2003), but mimics nonphotic phase resetting (Antle, Steen, & Mistlberger, 2001). A1R/A2AR antagonist caffeine dose-dependently reduces nonphotic phase resetting (Antle et al., 2001) and lengthens free-running circadian periods in mice (Oike, Kobori, Suzuki, & Ishida, 2011), although the mechanism by which this occurs is unknown.

Levels of extracellular adenosine vary in a circadian manner (Murillo-Rodriguez, Blanco-Centurion, Gerashchenko, Salin-Pascual, & Shiromani, 2004). As a product of ATP hydrolysis, the accumulation of extracellular adenosine is activity dependent (Pascual et al., 2005). Thus, the daily rise in adenosine concentration is thought to reflect the homeostatic need for sleep. However, circadian

variation in A1R and ENT1 expression in wake-promoting areas of the brain (Alanko, Stenberg, & Porkka-Heiskanen, 2003; Murillo-Rodriguez et al., 2004; Virus, Baglajewski, & Radulovacki, 1984) may indicate that they are targets of circadian timekeeping. Likewise, astrocytic release of ATP in the SCN follows a circadian pattern (Marpegan et al., 2011). The notion that a feedback loop may exist between the circadian and adenosinergic systems merits further exploration.

LOW ADENOSINE TONE IN ALCOHOL WITHDRAWAL-INDUCED INSOMNIA

The cost of alcohol-related sleep disorders in the United States exceeds US$18 billion per year (Brower, Aldrich, Robinson, Zucker, & Greden, 2001). In healthy people, ethanol decreases sleep latency, increases non-rapid eye movement (NREM) sleep, and suppresses, then increases, REM sleep during the first and second halves of sleep time, respectively. Patients in alcohol withdrawal experience severe insomnia, reduced NREM sleep, and increased REM sleep (Allen, Wagman, Faillace, & McIntosh, 1971; Brower, Aldrich, & Hall, 1998; Colrain, Crowley, Nicholas, Padilla, & Baker, 2009; Ehlers & Slawecki, 2000; Kubota, De, Brown, Simasko, & Krueger, 2002; Mukherjee, Kazerooni, & Simasko, 2008; Mukherjee & Simasko, 2009; Veatch, 2006), sleep impairments that may predict relapse (Brower & Perron, 2010). Animal models of withdrawal confirm increased wakefulness and lower total sleep time (Ehlers & Slawecki, 2000; Kubota et al., 2002; Mendelson et al., 1978; Mukherjee et al., 2008; Mukherjee & Simasko, 2009; Veatch, 2006).

Acute ethanol inhibits ENT1 in astrocytes to increase extracellular adenosine (Nagy, Diamond, Casso, Franklin, & Gordon, 1990), which induces sedation via inhibition of wake-promoting BF neurons (Thakkar, Engemann, Sharma, & Sahota, 2010). Altered adenosine signaling also contributes to sleep disruptions during withdrawal (Sharma, Engemann, Sahota, & Thakkar, 2010). Ethanol-dependent rats display increased wakefulness, reduced NREM and REM sleep, and more active wake-promoting BF neurons (Thakkar et al., 2010). They also lack the rise in BF adenosine during sleep deprivation and have lower BF expression of A1R and ENT1 (Sharma et al., 2010). Mice lacking ENT1 display reduced adenosine concentrations (Nam et al., 2011), lower ethanol sensitivity, and higher alcohol consumption versus wild types (Choi et al., 2004). Thus, diminished BF adenosine tone in withdrawal-induced insomnia may result from ENT1 and A1R downregulation. It is of great interest to determine whether gliotransmission is compromised in withdrawal-induced insomnia and to characterize the impact of ethanol-related circadian dysregulation on sleep homeostasis.

REGULATION OF ALCOHOL DRINKING BY ADENOSINE AND GLUTAMATE IN NEUROGLIAL INTERACTION

In the nucleus accumbens (NAc), adenosine activates presynaptic A1R to inhibit glutamate release (Harvey & Lacey, 1997), which is enhanced by acute ethanol during intoxication (Dunwiddie & Masino, 2001). In mice, ENT1 deletion reduces ethanol ataxia and hypnosis and increases alcohol drinking (Choi et al., 2004), while neuronal ENT1 overexpression increases ethanol intoxication (Parkinson et al., 2009). Several genetic variants of ENT1 are considered candidate genes for addiction (Hodgkinson et al., 2008) and are associated with alcohol abuse with poor sleep in women (Gass et al., 2010) and alcohol dependence with withdrawal seizures (Kim et al., 2011).

Altered glutamate neurotransmission in the NAc is one of the key neural mechanisms underlying the ethanol-dependent phenotype of ENT1-null mice. ENT1 deletion decreases adenosine levels, reducing presynaptic A1R-mediated inhibition of glutamate release (Choi et al., 2004) and decreasing expression of glutamate uptake transporter GLT-1/EAAT2 (Wu, Lee, Choi, Kim, & Choi, 2010). The resulting high glutamate levels in ENT1-null mice promote resistance to ethanol intoxication (Chen et al., 2010). Consistent with this evidence, N-methyl-D-aspartate receptor antagonist CGP37849 (Nam et al., 2011), antiglutamatergic medication acamprosate (Lee et al., 2011), or EAAT2 upregulator ceftriaxone (Lee et al., 2013) reduced alcohol intake by ENT1-null mice.

Interestingly, the intracellular consequences of high glutamate in ENT1-null mice are reductions in protein kinase Cγ-driven activation of neurogranin and Ca^{2+}/calmodulin-dependent protein kinase II, resulting in lower cAMP response element-binding protein (CREB) activity in the NAc core (Nam et al., 2011). CREB is a target of many drugs of abuse (Moonat, Starkman, Sakharkar, & Pandey, 2010), responsible for addiction-related changes in synaptic plasticity. The NAc core regulates motivation for conditioned stimuli (Everitt & Robbins, 2005), suggesting that reduced CREB activity in ENT1-null mice contributes to their deficient ethanol-induced conditioned place aversion (Chen et al., 2010). A2AR-mediated protein kinase A signaling also underlies excessive alcohol drinking in ENT1-null mice by enhancing reward motivation in operant paradigms (Nam et al., 2013).

EAAT2 AS A TREATMENT TARGET FOR ALCOHOL USE DISORDERS

Much literature implicates neuroglial mechanisms in the hyperglutamatergic brain state resulting from chronic alcohol exposure. In cultured astrocytes, ethanol increases glutamate uptake without affecting glutamate transporter

expression (Othman, Sinclair, Haughey, Geiger, & Parkinson, 2002; Smith, 1997). In vivo, however, as little as 1 week of moderate ethanol exposure decreases glutamate uptake in the rat NAc (Melendez, Hicks, Cagle, & Kalivas, 2005). Chronic ethanol self-administration for 20 months also downregulates glutamate transport in the cerebral cortex of ethanol-preferring (P) rats relative to ethanol-naïve controls (Schreiber & Freund, 2000). The discrepancy between studies may reflect differences in ethanol administration (continuous in cultured cells, but intermittent in rats), with the in vivo studies reflecting clinical observations of hyperglutamate levels in alcoholism.

EAAT2, expressed primarily by astrocytes (Anderson & Swanson, 2000; Rothstein et al., 1994), is responsible for the removal of ~90% of extracellular glutamate (Danbolt, 2001; Ginsberg, Martin, & Rothstein, 1995; Mitani & Tanaka, 2003; Rothstein, Van Kammen, Levey, Martin, & Kuncl, 1995). Accordingly, activation of EAAT2 expression/function may normalize hyperglutamatergic transmission. The murine EAAT2 (SLC1A2) gene is located near quantitative trait loci for neuroexcitability and seizure frequency in models of alcohol withdrawal and epilepsy (Crabbe & Belknap, 1993; Kirschner, Copeland, Gilbert, Jenkins, & Amara, 1994). EAAT2 is also implicated in models of morphine, methamphetamine, and cocaine addiction (Abulseoud, Miller, Wu, Choi, & Holschneider, 2012; Sari, Smith, Ali, & Rebec, 2009) and is linked with alcoholism in humans (Sander et al., 2000).

As the antibiotic ceftriaxone is a positive regulator of EAAT2 expression (Miller et al., 2008; Rothstein et al., 2005; Sari, Prieto, Barton, Miller, & Rebec, 2010; Sari, Sakai, Weedman, Rebec, & Bell, 2011; Sari et al., 2009), its effect on alcohol-related behavior and drinking was investigated in several studies. In P rats, ceftriaxone dose-dependently suppresses ethanol intake and upregulates EAAT2 in the prefrontal cortex (PFC) and NAc (Sari et al., 2011). Similarly, ceftriaxone-induced upregulation of EAAT2 in the PFC and NAc correlates with decreases in withdrawal symptoms and relapse-like ethanol drinking in P and Wistar rats (Abulseoud et al., 2014). Ceftriaxone also reduced ethanol intake by ENT1-null mice, elevating EAAT2 and water channel aquaporin 4 (AQP4) in ENT1-null mice (Lee et al., 2013). Disruption in AQP4 expression/function has been implicated in brain injury resulting from ethanol (Katada et al., 2012; Sripathirathan, Brown, Neafsey, & Collins, 2009) and other neurological disorders including ischemia (Taniguchi et al., 2000), edema (Vizuete et al., 1999), and neuromyelitis optica (Hinson et al., 2008). A role for AQP4 in alcohol intake remains to be discovered.

CONCLUSIONS

Neuroglial adenosine–glutamate interactions are essential in the maintenance of circadian rhythms, sleep, and the regulation of alcohol intake. Astrocytes play a key role in modulating these behaviors by releasing ATP and adenosine and taking up glutamate. As an endogenous sleep-promoting agent that is regulated by circadian and activity-dependent mechanisms, adenosine may represent a bridge between the circadian and homeostatic sleep systems. The role of adenosine in ethanol-induced sedation and alcohol withdrawal insomnia attests to the utility of targeting adenosine signaling to treat alcoholism. The importance of adenosine signaling to astrocyte function and alcohol intake is well supported by studies in mice lacking adenosine transporter ENT1. Although much remains to be discovered, compromised astrocytic function appears central to alcohol-induced pathophysiology, and enhancing EAAT2/AQP4 expression may be key to reducing alcohol drinking and relapse.

CONFLICT OF INTEREST

The author declares no financial interests or potential conflicts of interest.

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Chapter 36

Sleep Quality and Risk of Alcohol Misuse

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SLEEP AND ALCOHOL USE: ACUTE EFFECTS

Alcohol Use and Sleep Physiology

Sleep problems and alcohol misuse co-occur and exhibit a bidirectional causal relationship. Studies conclude that although the sedating properties of moderate to excessive alcohol intake initially help to reduce sleep onset latency (SOL), once metabolized it results in fragmented and deficient sleep. In the latter half of sleep the effects of intoxication result in inefficient sleep, stimulating wake after sleep onset, decreasing slow-wave sleep, and causing abnormalities in rapid eye movement (REM) periods (suppression of REM in the first half of sleep and rebounding in the second half of sleep) (Landolt, Roth, Dijk, & Borbély, 1996; MacLean & Cairns, 1982; Roehrs, Zwyghuizen-Doorenbos, Timms, Zorick, & Roth, 1989). At blood alcohol levels of 0.06–0.08, for example, sleep is disrupted once alcohol is eliminated from the body, roughly 4–5 h into the sleep cycle (Roehrs & Roth, 2001).

Recent evidence indicates that the effects of alcohol consumption on sleep may be modified by developmental age. In contrast to the current findings, Chan, Trinder, Andrewes, Colrain, and Nicholas (2013) found that alcohol did not result in reduced SOL or increased REM in the latter half of sleep in a sample of 18- to 21-year-old women. The authors contend that developmental changes in sleep cycles (e.g., delayed circadian timing and reduction in delta sleep) among late adolescents may result in a relationship between nightly alcohol consumption and sleep that is unique to this age group. Although more research is needed to investigate the unique processes by which alcohol directly affects sleeping cycles in nonadult age groups, the research specific to adults is conclusive: even at moderate levels of drinking, consuming alcohol prior to bedtime has adverse effects on sleep quality in adults. Other studies have also found that alcohol use prior to sleep suppresses growth hormone secretion, although the clinical consequences are not yet known (Ekman et al., 1996; Prinz, Roehrs, Vitaliano, Linnoila, & Weitzman, 1980).

Poor Sleep and Cognitive–Behavioral Functioning

Laboratory studies have also assessed the impact of sleep restriction and deprivation on human subjects' psychosocial and cognitive functioning after consuming alcohol. Relative to control participants, sleep-deprived participants exhibit diminished attention, increased risk-taking behaviors, and impairment of motor response from alcohol intake (Roehrs, Beare, Zorick, & Roth, 1994; Roehrs & Roth, 1998). In a study of young adult pilots, blood alcohol concentrations of 0.10–0.12 prior to sleep impaired performance, relative to a placebo, on a flight simulator 14 h later (Yesavage & Leirer, 1986). These findings are consistent with studies in which sleep deprivation impaired participants' executive functioning, including problem-solving, inhibitory functioning, and divergent thinking capacity (Linde & Bergström, 1992; Nilsson et al., 2005; Wimmer, Hoffmann, Bonato, & Moffitt, 1992).

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Further, brain studies link sleep deprivation with reductions in neural activity in the prefrontal cortex region of the brain, an area essential for higher-order executive functioning (e.g., decision making, self-monitoring, and conflict resolution; Thomas et al., 2000, 2003). Inadequate sleep may thus deprive people of important physical and cognitive capacities that are needed to evade potential harms and make rational and informed decisions while drinking. These laboratory-based findings raise awareness of the hazards of relying on alcohol to promote sleep as well as the risks associated with drinking while sleep-deprived, and inform the research and treatment of comorbid alcohol use and sleep disorders.

Daytime sleepiness combined with alcohol consumption appears to intensify the physiological effects of alcohol. Roehrs and Roth (1998) manipulated participants' nocturnal sleep durations and then administered alcohol the following day. Sleepiness and psychomotor performance assessments over 8 h supported the relationship between increased sleepiness at alcohol intake with poorer psychomotor functioning. Overall, a significant body of laboratory-based sleep research using simulated and computerized tasks as well as electrophysiological measures has shed light on the acute causal effects of the relationship (i.e., alcohol consumption on sleep quality and sleep quality on drinking impairment).

SLEEP AND ALCOHOL USE: BEHAVIORAL RISKS

Poor sleep is associated with alcohol misuse and problems among adolescents (Johnson & Breslau, 2001; Tynjälä, Kannas, & Levälahti, 1997), college students (Kenney, Lac, LaBrie, Hummer, & Pham, 2013), and adults (Chaput, McNeil, Després, Bouchard, & Tremblay, 2012). Furthermore, sleep problems have prospectively predicted alcohol misuse in community samples (e.g., Crum, Storr, Ya-Fen, & Ford, 2004; Weissman, Greenwald, Niño-Murcia, & Dement, 1997), relapse among alcoholics (e.g., Brower, Aldrich, & Hall, 1998; Brower, Aldrich, Robinson, Zucker, & Greden, 2001), and alcohol use among adolescents (sleep problems at age 3–5 years predicted early onset of alcohol use at age 12–14 years; Wong, Brower, Fitzgerald, & Zucker, 2004).

Adolescents

Sleep and alcohol problems are prevalent public health concerns in adolescent populations. Among elementary and high school students in the United States, more than one half report feeling tired or sleepy and more than one third reported problems staying asleep within the prior 2 weeks (National Sleep Foundation, 2006). Further, it appears that insufficient and inconsistent sleep patterns persist into college and emerging adulthood (Lund, Reider, Whiting, & Prichard, 2010). Underage alcohol misuse is also common in adolescents: 7 in 10 U.S. high school students report ever consuming alcohol, with about 1 in 5 reporting binge drinking (5+ drinks in a row) in the prior 2 weeks (Johnston, O'Malley, Bachman, & Schulenberg, 2011). Addressing heavy drinking is central to risk prevention; approximately 90% of all underage alcohol consumed is consumed while binge drinking, and bingeing increases exponentially risks for experiencing negative consequences (Office of Juvenile Justice and Delinquency Prevention, 2005).

In large studies of adolescents, those reporting higher levels of sleep problems also reported higher levels of risk-taking behaviors, particularly in late adolescence (Bailly, Bailly-Lambin, Querleu, Beuscart, & Collinet, 2004; O'Brien & Mindell, 2005; Taylor & Bramoweth, 2010). Among the most prevalent risk behaviors associated with poor sleep in this population is heavy drinking. Sleep disturbance is associated with alcohol problems, including drinking frequency, drinking quantity, and inebriation (Johnson & Breslau, 2001; Morioka et al., 2013; Vignau et al., 1997). In a recent nationally representative study of 98,867 Japanese adolescents, difficulty initiating sleep, difficulty maintaining sleep, and early morning awakening were associated with number of drinking days as well as amount of alcohol consumption per drinking occasion (Morioka et al., 2013). Moreover, adolescents report significantly greater prevalence of sleep problems even at moderate levels of drinking (i.e., less than 5 drinking days per month or less than a glass of alcohol per occasion compared to abstainers).

The relationship between sleep and alcohol problems among adolescents is particularly important in light of the change in central neuroendocrine regulation and neural maturation that occurs during this developmental age. These biological changes affect physiological, cognitive, and psychological functioning. Thus, at a time when sufficient sleep is critical to developmentally appropriate brain reorganization and recuperation (Feinberg & Campbell, 2013), adolescents tend to experience biological and social changes that counteract healthy sleep schedules. Puberty is associated with insomnia symptoms among adolescents (Bailly et al., 2004). In a study of 431 adolescents, Pieters, Van Der Vorst, Burk, Wiers, and Engels (2010) found that pubertal development was associated with sleep disturbance and preferences for later bedtimes, which in turn were predictive of alcohol use. Therefore, the pubertal development that occurs during adolescence may heighten risks for co-occurring sleep and alcohol problems, such that puberty predicts problematic alcohol use through altered sleep regulation and patterns.

Overall, sleepiness is associated with impaired executive functioning and cognitive control (e.g., impulsivity and attention control; Anderson, Storfer-Isser, Taylor, Rosen, & Redline, 2009; Beebe et al., 2008; Dahl, 1996), and excessive drinking during adolescence is linked to

deficits in neural and cognitive functioning, such as memory impairment (Acheson, Stein, & Swartzwelder, 1998; Brown, Tapert, Granholm, & Delis, 2000; Zeigler et al., 2005). More research examining the potential interaction or synergistic relationship between poor sleep and drinking on adolescent brain development is warranted.

College Students

In a nationally representative survey of 123,078 U.S. college students, over one quarter reported sleep difficulties as "traumatic or difficult to handle" in the prior 12 months, and 60% of students reported feeling "tired, dragged out, or sleepy" during the majority of days during a week (ACHA, 2013). Consistent with these reports, in other studies, 60–68% of students reported sleep problems (Hicks, Fernandez, & Pellegrini, 2001; Lund et al., 2010). Among young adults, sleep problems are linked to a range of negative consequences, including risk-taking behaviors (e.g., drowsy driving, violence, unsafe sex, substance use; O'Brien & Mindell, 2005; Taylor & Bramoweth, 2010; Wolfson & Carskadon, 1998) and poor academic performance (Buboltz et al., 2006; Gaultney, 2010; O'Brien & Mindell, 2005; Singleton & Wolfson, 2009). As many as 1 in 5 students report that sleep difficulties have a negative impact on their individual academic performance (e.g., lower grades, dropped courses; ACHA, 2013). During the college years, students are especially vulnerable to sleep problems (Tsai & Li, 2004) and risky alcohol use (Gaultney, 2010; Kenney et al., 2013; Thompson, Leinfelt, & Smyth, 2006). Social and academic demands, for instance, increase students' likelihood to manifest delayed sleep phase disorder (Kloss, Nash, Horsey, & Taylor, 2011).

In a 2012 study of college students (Kenney, LaBrie, Hummer, & Pham, 2012), poorer global sleep quality moderated the relationship between drinking and alcohol risk such that among heavier drinkers, participants reporting poorer (as compared to better) sleep quality experienced considerably greater levels of alcohol-related negative consequences. Especially in risky college drinking contexts, insufficient sleep may increase alcohol risk through its depletion of cognitive functioning (O'Brien & Mindell, 2005; Taylor & Bramoweth, 2010; Wolfson & Carskadon, 1998). Thus, drinking excessively when sleep-deprived appears to have a synergistic effect on exacerbating risks for alcohol-related negative outcomes. In this way, although intoxication itself weakens cognitive functioning, decision making, and self-protective abilities, co-occurring sleep deficiency may make arriving at safe decisions and warding off negative consequences all the more difficult. In contrast, lighter drinkers, even if deprived of quality sleep, may have less compromised cognitive functioning when drinking.

Studies examining the use of sleeping medication to induce sleep demonstrate that 10% of college students use prescribed and nonprescribed sleeping medication to facilitate sleep (McCabe, 2008). An estimated 10% of student drinkers in another survey reported using alcohol as a sleep aid in just the previous week (Taylor & Bramoweth, 2010). More large-scale epidemiological studies that assess students' reliance on sleeping medications or alcohol to fall asleep are warranted.

Insomnia and Alcohol Use in the General Population

Among people with persistent insomnia—typically defined as having significant difficulties initiating or maintaining sleep for more than 3 or 4 consecutive weeks (Stein & Friedmann, 2005)—nearly 1 in 3 report using alcohol as a sleep aid and, of those, 2 in 3 perceive alcohol as an effective means for inducing sleep (Ancoli-Israel & Roth, 1999). Among individuals with sleep problems, using alcohol to induce sleep is associated with higher levels of daytime sleepiness, over and above insomnia symptoms; total sleep time; and sociodemographics (Costa e Silva, Chase, Sartorius, & Roth, 1996). Paradoxically, despite alcohol's adverse effects on sleep overall, its ability to reduce SOL is a powerful mechanism by which individuals with sleep problems may become reliant on consuming moderate to excessive doses of alcohol as a sedative (Johnson & Breslau, 2001; Roane & Taylor, 2008; Roehrs & Roth, 2001). Risks associated with habitual alcohol-induced sleep include the need for higher doses of alcohol, as individuals build up tolerance within as short a period as 1 week.

In a general sample of non-alcohol-dependent individuals ($N = 1537$), those reporting sleep disturbances because of worry had double the risk for developing an alcohol use disorder one decade later (Crum et al., 2004). In a study of over 1000 young adults, those with (versus without) insomnia were significantly more likely to have an alcohol use disorder 3 years later (Breslau, Roth, Rosenthal, & Andreski, 1996). Large epidemiological community samples support the prospective relationship between insomnia and onset of alcohol abuse (Weissman et al., 1997).

Alcohol-Dependent Adults

Alcohol and sleep disorders are highly comorbid (Teplin, Raz, Daiter, Varenbut, & Tyrrell, 2006; Weissman et al., 1997). In general samples of adults, rates of alcohol abuse are twice as high among individuals with, relative to without, insomnia (7% vs 3.8%; Ford & Kamerow, 1989). In their examination of 11 studies, Zhabenko, Krentzman, Robinson, and Brower (2013) calculated that, on average, 59.4% of 3027 alcohol-dependent patients experienced symptoms of insomnia. These prevalence rates are nearly twice that of general population samples (Calem et al., 2012; Roth et al., 2006).

For alcohol dependents, alcohol withdrawal is associated with severe disturbances in sleep, including longer sleep latency, increased nighttime disruptions, poor sleep efficiency, and reductions in REM rebound in the latter half of sleep (Gillin, Smith, Irwin, Kripke, & Schuckit, 1990; Thompson, Gillin, Golshan, & Irwin, 1995). Among patients in remission from alcohol use disorders, self-reports indicate that serious sleep problems may endure for up to 6 months (Brower, Krentzman, & Robinson, 2011; Currie, Clark, Rimac, & Malhotra, 2003), and abnormal polysomnography (PSG) readings may persist for years in abstainers (Drummond, Gillin, Smith, & DeModena, 1998). Reasons for this persistence may include cumulative alcohol toxicity, mental health comorbidities, or a sleep disorder (e.g., insomnia) that preceded alcohol dependence (Zhabenko et al., 2013).

Particularly concerning is that sleep problems are a common risk factor for relapse among alcohol dependents (Teplin et al., 2006). Whether assessed using PSG techniques in laboratory settings (Drummond et al., 1998; Gillin et al., 1994; Teplin et al., 2006) or subjective self-reports (Brower et al., 1998; Brower et al., 2001; Conroy et al., 2006), difficulty or increased time needed to fall asleep and sleep disturbances (e.g., frequent awakenings or movements during sleep) consistently predict relapse in alcohol-dependent patients. Alcohol-dependent patients who report insomnia or difficulty falling asleep are up to twice as likely to relapse within 6 months compared with patients without sleep difficulties (Brower, 2003; Brower et al., 1998). In samples of alcohol dependents, 58–91% report serious sleep problems or insomnia during the first week of detoxification (Cohn, Foster, & Peters, 2003; Foster, Marshall, & Peters, 2000; Mello & Mendelson, 1970). Although the specific causal mechanisms leading to relapse are not fully established, many alcohol-dependent patients admit to drinking as a sleep aid despite recognizing that it disturbs their sleep (Mackenzie, Funderburk, & Allen, 1994). In all, given that sleep problems are a strong predictor of relapse, successful recovery from alcohol dependence may require careful monitoring, and appropriate treatment of sleep disturbances should be monitored.

Treating Sleep Problems in Alcohol Dependents

Untreated sleep problems pose a primary impediment to healthy recovery among alcohol dependents, particularly in the first several months of withdrawal (Brower et al., 1998; Brower et al., 2001). To date, a number of pharmacological and nonpharmacological behavioral treatments aimed at managing severe sleep problems have demonstrated efficacy in this population. Given patients' susceptibility to substance abuse and the risk for overdose when hypnotic medications are mixed with alcohol, clinicians must use caution when prescribing treatment. In a recent survey, 64% of addiction treatment specialists reported treating alcohol-dependent insomniac patients with pharmacological agents and less than one quarter did so with the majority of these patients (Friedmann et al., 2003).

Nonpharmacological cognitive behavioral treatments for insomnia (CBT-I) have demonstrated efficacy in non-alcohol-dependent patients (Irwin, Cole, & Nicassio, 2006; Smith et al., 2002). Moreover, CBT-I is found to be more beneficial than pharmacological treatments over 6–8 weeks (Jacobs, Pace-Schott, Stickgold, & Otto, 2004; Sivertsen, 2006; Smith et al., 2002). The efficacy of CBT-I may be explained, in part, by the robust role of sleep-related cognitions in remission. Sleep cognitions are strongly tied to sleep disturbance onset and maintenance (Harvey, 2002) and appear more influential on sleep problems than physiological arousal (Lichstein & Rosenthal, 1980). Cognitive beliefs may include the inability to calm a racing mind (Espie, Brooks, & Lindsay, 1989). Overall, CBT-I interventions targeting alcohol-dependent insomniacs have been effective in improving sleep, but have not yielded consistent reductions, relative to controls, in rates of relapse (Arnedt et al., 2007; Arnedt, Conroy, Armitage, & Brower, 2011; Currie, Clark, Hodgins, & El-Guebaly, 2004). More research is needed to determine if CBT-I can be effectively tailored to recovering alcohol-dependent patients to reduce the risk for relapse.

CONSIDERATIONS FOR FUTURE RESEARCH

Longitudinal Studies

Methods that enable researchers to better assess the causal relationship between sleep and alcohol risk are needed to better inform clinical practice. Daily diary data collection minimizes retrospective self-report and allows for daily prospective data reports. Ecological Momentary Assessment (EMA; Stone & Shiffman, 1994) is an example of an innovative data collection application that enables participants to provide data on their current drinking behaviors, in real time and in natural drinking environments, using cell phones or other mobile devices. EMA may be a convenient and reliable way for participants to provide daily information on the prior night's sleeping as well as drinking behaviors that following day. In addition to explicating the causal relationship between sleep and alcohol problems, prospective and longitudinal studies enable researchers to best identify predictors and moderators of sleep and alcohol disorders in order to shed light on how co-occurring disorders evolve over time.

Measuring Sleep and Alcohol Use Problems

Existing studies examining the relationship between sleep and alcohol behaviors use a variety of measures to assess

sleep and alcohol-related behaviors and diagnoses. With respect to both collection (e.g., subjective self-report, objective PSG) and variable operationalization (definitions and time frames), there is a lack of standardized measurement. In order to gain a consistent understanding of the relationship between sleep and alcohol risk and enable the comparison across populations, coordinated and consistent assessment techniques using established and validated instruments are needed.

Mental Health

To fully disentangle the risks associated with sleep and drinking behaviors, it is important for researchers to examine potential moderating or confounding variables. Poor sleep (Benca, Obermeyer, Thisted, & Gillin, 1992; Kenney et al., 2013; Taylor, Bramoweth, Grieser, Tatum, & Roane, 2013; Taylor, Lichstein, Durrence, Reidel, & Bush, 2005) and problematic alcohol use (Bellos et al., 2013; Davidson, 1995; Merikangas, Angst, Eaton, & Canino, 1996; Murray et al., 2012) are strongly correlated with depression and anxiety symptoms. Sleep disturbances prospectively predict the development of psychological disorders (e.g., major depression) 1–3 years later in general adult samples (Breslau et al., 1996; Ford & Kamerow, 1989) and up to 7 years later in adolescent samples (Roane & Taylor, 2008; Roberts, Roberts, & Chen, 2002). Therefore, it is important for research to account for coexisting mental health problems when examining the influence of sleep deprivation on alcohol risk.

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Chapter 37

Sleep and Addictions: Linking Sleep Regulation with the Genesis of Addictive Behavior

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INTRODUCTION

The main mystery about sleep is why we do not do more of it. Almost every type of human function or dysfunction involves sleep disruption, from our perception of sleep as an impediment to our social and professional lives, thus directing our schedules to restrict the time we allocate for sleep; to psychiatric disorders, the majority of which interfere with sleep patterns. This is even more enigmatic considering the overlap between sleep regulatory mechanisms and reward systems, as will be outlined here. Like the majority of psychiatric disorders, sleep disturbances are a central feature of addictions, with different substances associated with divergent effects on sleep regulation and subjective sleep quality. Clearly, the long- and short-term pharmacological effects of a psychoactive drug alter the functionality of brain systems associated with arousal states; hence, it would be expected that continued use of such substances would impact sleep patterns. However, the links between the motivational effects of drug use and sleep are far more complex. I propose a model that will demonstrate that key mechanisms involved in the susceptibility to engage in drug-seeking behaviors and to develop an addiction are linked to sleep and sleep disruption. The emerging model suggests that the same systems that reinforce drug-seeking behaviors are also activated during sleep. As replay patterns during sleep have been linked to consolidation of memories, sleep, per se, may have a role in the creation of addiction. With this in mind, the proposed model may also provide a tentative answer to the questions posed, suggesting that sleep deprivation, at least in a mild form, is reinforcing.

SLEEP PATTERNS

Sleep patterns vary on two major dimensions that reflect the two systems that regulate sleep behavior, namely, sleep timing and sleep depth. Both, and each on its own, contribute to subjective sleep quality, whereby frequent awakenings or insufficient time available for sleep are associated with poor subjective sleep quality and daytime fatigue. Briefly, sleep consists of two discrete states defined as rapid eye movement (REM) sleep that constitutes 18–25% of adult sleep time and non-REM (NREM) sleep. Sleep typically progresses in a cyclic manner from lighter NREM stages to deeper NREM sleep to REM sleep, with each cycle approximately 80–120 min long. The different stages are characterized by

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unique electroencephalographic (EEG) patterns, with deeper NREM sleep stages associated with increasingly slower EEG waveforms. Stage II EEG is also characterized by the hallmark K-complexes[1] and spindles[2], and the slowest, delta frequency (0.5–4 Hz) waves predominate stages III/IV of NREM sleep, also referred to as slow-wave sleep (SWS). REM sleep derives its name from the periodic bursts of eye movements but is also defined by almost complete loss of muscle tone and high-frequency EEG in the beta (15–30 Hz) and gamma (30–80 Hz) ranges. During the length of the sleep period, the amount of slow waves declines, whereas stage II and REM dominate the latter half of the night.

The EEG patterns seen in the different states are driven by distinct neuronal systems. Concisely, during waking, high-frequency desynchronized cortical activity reflects arousing signals originating from the brain stem reticular activating system, midbrain monoaminergic projections, cholinergic projections from the pontine tegmentum and basal forebrain, and hypothalamic arousal signals including hypocretin and histamine. During NREM sleep, these systems are largely quiescent due to GABAergic inhibition generated from the ventrolateral preoptic area (VLPO). This inhibition disengages the thalamus and cortex from external stimulation, resulting in the above-mentioned spindles and slow oscillations. The slow oscillations are the manifestation of intracortical fluctuations in membrane potential of neurons, shifting synchronously between a depolarized "up" state and a hyperpolarized "down" state. Transitions between wake and sleep are mediated by reciprocal inhibition between the VLPO and arousing centers in the brain stem and hypothalamus, modeled as the "flip-flop switch" (Saper, Scammell, & Lu, 2005). A central regulator of arousal states (also involved in feeding and motivational behaviors) is the hypocretin/orexin system. Hypocretin cell bodies are located in the lateral hypothalamus and project to prefrontal regions, limbic structures (e.g., hippocampus, amygdala), midbrain monoaminergic nuclei including dopamine centers, and the pedunculopontine tegmental nucleus (PPT) and laterodorsal tegmental nucleus (LDT) involved in REM (Pace-Schott & Hobson, 2002; Tsujino & Sakurai, 2009).

During REM sleep, mesopontine LDT/PPT and forebrain cholinergic systems are reengaged. "REM-on" cell groups in the LDT/PPT control the initiation and maintenance of REM, including the tonic increase in reticular, thalamocortical, and cortical neuronal firing rates, resulting in high-frequency EEG activity, the characteristic eye movements, and muscle atonia (Jones, 2000).

1. A singular occurrence of a slow wave consisting of a negative high-voltage peak, usually greater than 100 μV, followed by a slower positive peak a similar magnitude.

2. A 0.5- to 3-s-long burst of sigma, 11- to 15-Hz, activity.

Sleep timing, architecture (distribution of stages), and depth are primarily regulated by circadian and homeostatic processes, which are discussed next.

Circadian Regulation of Sleep

The circadian system (termed "process C") is an endogenously generated 24-h rhythm, which persists in the absence of external cues, impacting most physiological and cognitive processes. In mammals, the circadian clock is maintained by the suprachiasmatic nucleus (SCN), located in the anterior hypothalamus, receiving photic input from the retina via the retinohypothalamic tract. On the molecular level, circadian rhythms are maintained by several core "clock" genes, expressed in most cell types. These genes code for transcription factors that regulate their own expression in a negative transcriptional–translational feedback loop, which also maintains an approximate 24-h oscillation (Schibler & Sassone-Corsi, 2002). In addition to the core genetic mechanism, evidence suggests that cellular metabolic processes also have a role in maintaining circadian rhythms (O'Neill et al., 2011). While molecular and cellular rhythms occur independently in all tissue types, in vivo the SCN is necessary for maintaining different organ systems in phase with each other (Dibner, Schibler, & Albrecht, 2010).

The SCN controls rest–activity cycles via projections to brain regions that regulate sleep and wake but is also reciprocally influenced by levels of arousal. For example, the SCN receives serotonergic projections from the raphe nucleus (Moore, Halaris, & Jones, 1978), which mediate the phase shifting effects of locomotion and prolonged wake periods (Kennaway, 2004). Thus, the circadian phase adapts to external cues, most robustly daylight, but also to exercise, feeding regimens, social cues, temperature, etc. (Mistlberger & Rusak, 2005). Accordingly, altered arousal and/or irregular social schedule may be key to comorbid sleep disruption seen in several disorders, including addictions, wherein arousing reward-related cues shift the circadian phase resulting in sleep disturbance.

Some, but not all, aspects of sleep are modulated by the circadian system. Mainly, the proportion of the sleep cycle spent in REM sleep is modulated by circadian processes, with higher proportions expressed in the latter part of the rest phase independent of how much sleep was attained earlier (e.g., Carskadon & Dement, 2000). Conversely, NREM slow-wave activity (SWA) increases with prior wake duration and declines during sleep episodes, with only minor modulation by circadian process (Dijk, 2009), and is therefore seen as a marker of homeostatic sleep processes.

Homeostatic Regulation of Sleep

The homeostatic process (termed "process S") represents the need for sleep that increases during wakefulness,

making sleep more difficult to resist, and decreases during sleep eventually invoking wake.

The hallmark of the homeostatic process is the amount and amplitude of delta waves in NREM sleep, quantified using spectral analysis algorithms such as the fast Fourier transform (FFT), which yields an energy per Hz (or power) index for all EEG waveforms. The power in the slow, delta frequency range positively correlates with the duration of prior waking and negatively correlates with prior sleep amount (Achermann & Borbely, 2003).

It is noteworthy that the changes in sleep patterns after sleep deprivation vary with the duration of sleep loss. Increases in NREM sleep delta power occur after relatively brief periods of sleep deprivation (e.g., 6–72 h). However, animals that were denied sleep for several weeks displayed mainly a rebound of REM sleep (Rechtschaffen, Bergmann, Gilliland, & Bauer, 1999). Potentially the lagging homeostatic build-up of REM sleep need is due to the fact that REM constitutes a smaller portion of sleep than NREM stages, and hence the rate of homeostatic pressure to compensate for lost REM is slower.

Unlike NREM sleep, lost REM sleep is compensated for by increasing the amount of REM. As overall sleep time tends not to increase significantly after sleep deprivation, REM sleep displaces NREM sleep under high homeostat REM sleep pressure. In addition, pressure for the expression for REM seems to build up within the sleep cycle, during NREMS (Benington & Heller, 1994; Franken, 2002). Whether this reflects a homeostatic process or the brain maintaining a balance between quiescent and active states (e.g., Drucker-Colin, 1995) remains to be determined.

The interplay between the circadian pacemaker and homeostatic control of sleep contributes to the consolidation of the sleep period and the differential distribution of the NREMS and REMS across the 24-h period. If the capacity to synchronize multiple physiological cycles is hampered, the ability to maintain consolidated sleep during the night could be reduced; resulting in diminished arousal levels during the day due to lack of good-quality sleep. In the long run, such individuals would accumulate sleep debt, which would potentially impair cognitive, emotional, and physiological functions.

Effects of Daytime Activities on Sleep Regulation

Beyond sleep homeostasis, sleep quality is influenced by numerous other factors. Individual differences in homeostatic regulation of sleep (Aeschbach, Cajochen, Landolt, & Borbely, 1996) and the degree of functional impairment after sleep deprivation (van Dongen, Baynard, Maislin, & Dinges, 2004) indicate genetic control of these traits (Franken, Chollet, & Tafti, 2001). Sleep architecture and EEG also change with age (e.g., Ohayon, Carskadon, Guilleminault, & Vitiello, 2004), neuropsychiatric disease (e.g., Riemann, Berger, & Voderholzer, 2001), developmental interventions (e.g., Hairston, Heller, & Sapolsky, 2000; Tiba, Palma, Tufik, & Suchecki, 2003), or acute stress (e.g., Meerlo, de Bruin, Strijkstra, & Daan, 2001).

But mainly the notion that sleep is associated with offline network remodeling, leading to memory retention, has led researchers to link EEG changes in sleep with behavioral plasticity. Indeed, some forms of learning have been found to influence SWA (e.g., Huber et al., 2008; Mascetti et al., 2013), spindle activity (Gais, Molle, Helms, & Born, 2002), and the amount of REM sleep (e.g., Hairston et al., 2005; Smith & Rose, 1997). It is today commonly assumed that experience-dependent neural plasticity during sleep is integral to global processes of memory consolidation.

Plasticity and Sleep Homeostasis

For the most part, the relationship between waking activity and EEG during sleep is correlational, with mechanistic hypotheses linking EEG phenomena with learning focused essentially on SWA in NREM sleep. Several mechanisms for the transduction of waking activities into increased slow waves have been proposed, the different perspectives all assuming a *use*-dependent system, implying that SWA helps adjust imbalances accrued in brain neural systems during prior wake. Among these hypotheses are *the adenosine hypothesis*, according to which use-dependent dephosphorylation of adenosine triphosphate (ATP) and adenosine diphosphate (ADP) during wakefulness causes the accumulation of adenosine; which, in turn, hyperpolarizes cortical neurons resulting in slow oscillations and neural synchrony (Benington & Heller, 1995; Thakkar, Winston, & McCarley, 2003). *The somnogenic trophic factor hypothesis* postulates that increases in somnogenic trophic factors, over time, modify levels of activity in neural circuits involved in sleep regulation, causing a transition to sleep (Krueger, Huang, Rector, & Buysse, 2013). *Metabolic perspective* links metabolic demand with molecular circadian signaling, to regulate rest–activity cycles (Franken, 2013).

The more relevant model in this context is *the synpatic homeostasis hypothesis* that posits the processing of ongoing information causes excitatory changes to cortical circuitry during wakefulness, leading to a "net" increase in synaptic strength; SWA reverses this process by actively promoting a generalized decrease in synaptic strength (Tononi & Cirelli, 2006). Thus, SWA is the homeostatic response to increased synaptic excitation accrued during waking activity. The hypothesis is based on the concept of "synaptic scaling," a novel plasticity mechanism that maintains a balance between excitatory and inhibitory activity in the context of fluctuating synaptic strength due to external (or internally driven) stimulation (Turrigiano, 2011). Despite some theoretical limitation of the hypothesis (see Frank, 2013; Siegel, 2005), a reliably supported prediction is that local increases

in SWA during NREM sleep will be found in regions that underwent synaptic modifications during recent wake (e.g., Huber, Ghilardi, Massimini, & Tononi, 2004; Vyazovskiy, Borbely, & Tobler, 2000).

As we will presently see, plasticity processes are highly relevant to the process of developing addictions, thus providing a link with sleep regulatory mechanisms. The following sections will first introduce relevant theories for the development of addictions, and then focus on the phenomenological relationship between addictions and sleep, detailing neural plasticity as a potential mechanistic link between the two systems.

MECHANISMS OF ADDICTION

The process of becoming addicted is not instantaneous and requires that the user experience the reinforcing effects of the drug repeatedly over a period of time. And even then, many users can maintain a level of recreational use, while others will develop dependency. The addicted individual continues to abuse substances, finding it difficult or impossible to change his/her behavior despite the dire consequences to physical and mental health, social, and economic functioning. Who are the individuals that become addicted? And which processes underlie the onset of addictions? This section will focus on two models for the development of addiction—*negative affect regulation* and *reward sensitivity*.

Negative Affect Regulation

Negative affect (NA) covers several aversive mood states, including anger, guilt, fear, and nervousness, that influence cognition, self-concept, and worldview. Individuals differ in trait levels of negative affectivity, with some individuals predisposed to experiencing more negative emotions, even in the absence of an external stressor. As the instantaneous reaction to an emotionally evocative stimulus is not always desirable, modifying the elicited emotions using cognitive reassessment processes enables us to regulate these responses (Gross, 1999). Individuals who have difficulty regulating their negative emotions, repeatedly experiencing exaggerated NA, may—over time—develop pathologic anxiety and depression (Davidson, 2002). Thus, affect regulation, especially the ability to regulate NA, refers to the mechanisms involved in adjusting our emotional states to intensity levels that are conducive to optimal function. A convergence of neuroimaging, neuropathological, and lesion studies has identified the networks involved in the regulation of emotional behavior. These include the limbic-cortical-striatal-pallidal-thalamic circuit, with multiple connections with the orbital and medial prefrontal cortex (Phillips, Ladouceur, & Drevets, 2008). Not surprisingly, this network is also involved in the development of addictions.

According to models of addiction, drug preference is linked to its ability to attenuate or avoid unpleasant emotions (Spada & Wells, 2009), suggesting that individuals who develop substance dependencies initially had difficulty downregulating NA. Indeed in adults, various measures of NA (e.g., neuroticism, depressive and anxiety symptoms) are correlated with excessive use of alcohol (Hartka et al., 1991), cannabis (White, Xie, Thompson, Loeber, & Stouthamer-Loeber, 2001), and nicotine (Degenhardt & Hall, 2001), as well as diagnoses of abuse or dependence on alcohol (e.g., Conway, Swendsen, Rounsaville, & Merikangas, 2002). Similar findings have been reported for adolescents, 18 years and younger, wherein measures of negative affectivity were correlated with the use of alcohol (e.g., White et al., 2001).

Reward Sensitivity

The concept of reward sensitivity originates in Gray's Reinforcement Sensitivity Theory (Gray & McNaughton, 2000) which focuses on personality determinants that explain individual differences in the motivational impact of reward and punishment. The model defines three motivational systems, a behavioral activation system (BAS), a fight-flight-freeze system (FFFS), and a behavioral inhibition/regulation system (BIS). BAS is responsible for organizing behaviors in response to appetitive rewards or relief from punishment, thereby increasing the propensity to engage in the ongoing behavior, and is postulated to underlie trait impulsivity and positive affect. Neurobiologically, BAS traits are associated with functionality of the central reward system, specifically projections from dopamine nuclei in the midbrain to the dorsal and ventral striatum, and their corresponding cortical projections to the prefrontal cortex (Depue & Collins, 1999; Knutson & Cooper, 2005). Thus, BAS traits (e.g., impulsivity, sensation seeking), which increase reward pursuit overriding risk-assessment of long-term consequences, have been the main focus of addiction research. Indeed, behavioral traits related to BAS positively correlate with problem drinking in nonclinical samples (Loxton & Dawe, 2001), and the presence of a lifetime alcohol abuse disorder in a community-based study (Johnson, Turner, & Iwata, 2003).

The FFFS incorporates emergency reactions occurring in the presence of threat cues (unconditioned or conditioned) and as such is related to NA. The BIS's role is more regulatory, resolving competition between rewarding and threatening stimuli. Neurobiologically, individual variation in BIS is correlated with differential activation and structure in limbic regions (Cherbuin et al., 2008; Cunningham, Arbuckle, Jahn, Mowrer, & Abduljalil, 2010).

Simply put, punishment avoidance and NA relates to FFFS/BIS functioning, while reward seeking is related to BAS functioning. Idiosyncrasies in NA and sensitivity to the rewarding effects of drugs may help explain individual differences in initial drug-seeking behaviors. But can these mechanisms also explain the development of dependence? The answer to this is better framed within the context of the

neurobiological changes that occur with repeated exposure to substances of abuse.

Neurobiological Models of Addictions—The Role of Plasticity

Neurobiological addiction models expand on the BAS framework, suggesting that drug-seeking behaviors are initially positively reinforced by the pharmacological effects of the substance ("liking"), which stimulates dopamine release in reward centers in the brain, thereby reinforcing cue-induced behavioral approach tendencies. With repeated exposure, cues related to the drug become more potent motivational forces, causing escalation in use ("behavioral sensitization"). Greater drug exposure leads to neurobiological changes that result in tolerance and withdrawal, wherein the rewarding effects of the drug are due to relief from symptoms of withdrawal or unpleasant craving-related arousal ("wanting"; Le Moal & Koob, 2007).

Indeed, independent of drug type, substance dependence is associated with structural and functional changes in the brain's reward system. Dopamine cell bodies originate in midbrain substantia nigra (SN) and ventral tegmental area (VTA), projecting to the dorsal and ventral striatum (respectively), the prefrontal cortex, hippocampus, and amygdala. This circuit acts in concert with projections from cortical regions, the hypothalamus, amygdala, and hippocampus, to regulate responses to naturally occurring reinforcers such as food, as well as to drugs of abuse. Dopamine release in target sites is regulated by several neurotransmitter systems including adenosine, gamma-aminobutyric acid (GABA), opiate, and nicotine receptors (Figure 37.1).

The dopaminergic mesolimbic system is critical both for the acute rewarding effects of stimuli and for associative learning linking environmental, or contextual stimuli, with the drug (Everitt, Dickinson, & Robbins, 2001). The transition to an addicted state, characterized by escalation in consumption and increased craving, requires neuroplastic changes in the relevant circuitry. Thus, symptoms of withdrawal, such as dysphoria and increased anxiety, most likely involve downregulation of activity of the reward system, combined with sensitization of brain stress-related neurocircuitry; while preoccupation with the drug and anticipation of its effects ("craving") involve the interaction of the extended amygdala, nucleus accumbens (NAcc), thalamus, and the prefrontal cortex. Once neural changes have occurred, anxiety and dysphoric mood increase the craving for the substance previously associated with euphoria and its anxiolytic effects (Kalivas & Volkow, 2005; Le Moal & Koob, 2007). The escalation of drug-seeking behaviors (behavioral sensitization) is likely mediated by plasticity in the NAcc, wherein dopamine release confers greater incentive salience to cues associated with the drug, thereby increasing craving in the presence of such cues. Studies have found that continued drug involvement causes changes in activity in the dorsal striatum and cingulate and medial prefrontal cortex (Feltenstein & See, 2013; Self, 2004), the latter resulting in deficits in decision-making and behavioral control (Feltenstein & See, 2013), behavioral traits linked to the BAS.

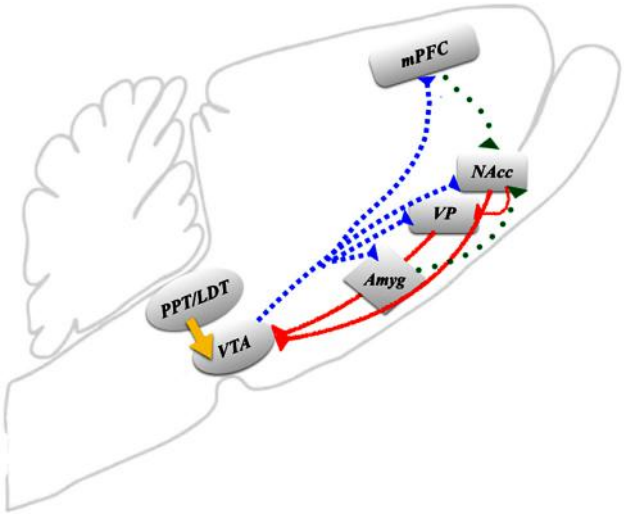

FIGURE 37.1 Selected elements and connectivity of brain reward circuitry. The rewarding effects of stimulants (e.g., amphetamine and cocaine) are mediated by inhibition of dopamine transporter in the NAcc, causing increased synaptic dopamine levels. Caffeine inhibits adenosine A_{2A} receptors, which colocalize with D2 receptors in the striatum, thereby increasing D2/D3 receptor availability in the NAcc, which also decreases tiredness. Nicotine acts on nicotinic cholinergic receptors on cell bodies in the VTA and terminals of mesolimbic dopamine neurons, resulting in increased dopamine release in NAcc. Nicotinic projections to the VTA include cells from the PPT/LDT nuclei involved in the regulation of REM sleep. The rewarding effects of electrical stimulation of the lateral hypothalamus, where hypocretin cell bodies reside, are likely mediated by activation of wake on/REM on neurons in the PPT (Tsujino & Sakurai, 2009). The amygdala also indirectly modulates VTA activity via the PPT and/or the lateral hypothalamus. Two GABAergic projection neurons from the NAcc to (A) the ventral pallidum (VP) and (B) the SN/VTA. GABAergic neurons in VP also project to SN/VTA. Thus, inhibitory output from the NAcc results in a negative feedback loop reducing dopamine activity in the NAcc. Phencyclidine (PCP) blocks N-methyl-D-aspartate (NMDA)-type glutamate receptors in NAcc, which reduces the excitatory input to GABAergic output neurons, thereby reducing self-inhibition mediated by the NAcc. Similarly, electrical stimulation of mPFC increases glutamate release in the VTA, stimulating the release of dopamine in the NAcc. Heroin and morphine disinhibit dopamine release in the NAcc, via inhibition of GABAergic cells. Dopamine projections are in dashed blue lines; glutamatergic input to the mesolimbic reward system is in dotted green; GABAergic projections in solid red; cholinergic input from the PPT is a solid yellow arrow. mPFC, medial prefrontal cortex; NAcc, nucleus accumbens; VP, ventral palludum; VTA, ventral tegmental area; SN, substantia nigra; PPT, pedunculopontine tegmental nucleus; LDT, laterodorsal pontine tegmental nucleus; Amyg, amygdala; REM, rapid eye movement.

Converging experimental evidence suggests shared signaling pathways for mechanism of neural plasticity (long term potentiation (LTP), and long term depression (LTD)) and addictions (e.g., Ikemoto, 2010; Self, 2004). It has been proposed that synaptic adaptation that occurs in the NAcc, after repeated drug administration, reflects synaptic scaling

processes, where general decreases in NAcc excitability during withdrawal trigger lasting compensatory changes in excitatory synapses. Although this hypothesis is yet to be tested directly, molecular changes underlying synaptic scaling have also been reported in drug exposure (reviewed in Thomas, Kalivas, & Shaham, 2008).

In conclusion, individual differences in NA and sensitivity to reward may help explain why some individuals engage in drug-seeking behaviors and have difficulty withstanding craving and withdrawal. Neural plasticity processes are involved in the development of addiction by shifting the homeostatic "set point" for dopamine activity in the striatum.

LINKING SLEEP AND SLEEP DIFFICULTY WITH ADDICTION PATHWAYS

Potentially, sleep is involved in addiction processes on three levels. First, sleep disturbances are linked to psychopathology in general and substance misuse in particular, via their effect on mood and affect regulation. Second, neurobiologically, sleep regulatory processes share substrates with systems associated with the development of addictions. The final section will focus on regulatory processes of sleep that have been shown to be important for neural plasticity, proposing a model wherein sleep may play a role in promoting the plastic changes that occur in the development of addiction.

Sleep Disturbances and Addictions

Sleep Disturbance and NA

There is an abundance of evidence linking sleep disturbances with mood and anxiety disorders (e.g., Ohayon & Roth, 2003) and general affect dysregulation (e.g., Bower, Bylsma, Morris, & Rottenberg, 2010; Zohar, Tzischinsky, Epstein, & Lavie, 2005). The relationship between waking affective states and sleep is clearly bidirectional. On the one hand, affective states impact sleep quality, whereby positive mood is associated with better objective and subjective sleep quality (Berry & Webb, 1985; Steptoe, O'Donnell, Marmot, & Wardle, 2008), and negative affective states are correlated with disrupted sleep patterns (e.g., McCrae et al., 2008).

Specific changes in sleep patterns may be driven by activation of neural systems associated with emotional arousal such as the cingulate cortex, insula, and amygdala (Murphy et al., 2009; Rolls, Inoue, & Browning, 2003). In fact, amygdala activity is closely associated with REM expression (e.g., Sanford, Tang, Ross, & Morrison, 2003; Tang, Yang, Liu, & Sanford, 2005), mediated by its interconnections with sleep regulatory regions including the cholinergic neurons in the basal forebrain, VLPO, and monoaminergic nuclei in the brain stem reticular formation. It also shares reciprocal connections with the REM-on centers in the pons (Germain, Buysse, & Nofzinger, 2008). Further, REM sleep characteristics are linked to the consolidation of amygdala-dependent learning (Pare, 2003; Walker & van der Helm, 2009), which may explain why increased REM amounts predict reinstatement of drug-seeking behaviors (i.e., relapse; Clark et al., 1998).

On the other hand, there is substantial evidence that sleep plays a central role in the regulation of affect (Walker & van der Helm, 2009). For example, Yoo, Gujar, Hu, Jolesz, and Walker (2007) found that sleep deprivation resulted in increased activation in the amygdala to negative emotional stimuli and dampened functional connectivity with the medial prefrontal cortex (Yoo et al., 2007). Thus, sleep deprivation both enhanced evoked NA associated with negatively valenced stimuli (see also Rosales-Lagarde et al., 2012) and impaired the capacity to downregulate this emotional response[3].

These findings imply that sleep is important for the ability to regulate the salience of cues that evoke NA. Specifically, cues linked with a drug of abuse may elicit a more potent motivational drive in the sleep-deprived individual, making him/her more likely to engage in substance-seeking behaviors. Indeed, sleep difficulty has been found to be a strong predictor of relapse (Brower, Aldrich, Robinson, Zucker, & Greden, 2001; Hairston, Akbar, & Conroy, 2013), especially elevated levels of REM sleep (Clark et al., 1998).

Sleep Disturbance and BAS

Studies also indicate a relationship between sleep disturbances and traits associated with BAS. For example, insomnia and daytime sleepiness were associated with impulsivity in a cohort of college students (Schmidt, Gay, & Van der Linden, 2008); and in adolescents, sleep difficulty was associated with attention problems (Fernandez-Mendoza et al., 2010) and higher frequency of externalizing problems, such as alcohol and substance use (Johnson & Breslau, 2001). Further, acute sleep deprivation was associated with risky decision-making (Acheson, Richards, & de Wit, 2007; Killgore, 2007), while neural response to reward anticipation in the dorsal striatum was positively correlated with subjective sleep quality (Holm et al., 2009).

A series of studies by Volkow and colleagues (Volkow et al., 2008, 2009, 2012), using positron emission tomography, found downregulation of dopamine D2/D3 receptors in the ventral striatum after one night of sleep deprivation and that these changes were associated with impaired performance on a visual attention task. This suggests that prolonged wake activates synaptic mechanisms that reduce sensitivity to dopamine, similar to the changes observed after repeated drug use. These findings may help explain why sleep disturbances are associated with BAS-related behaviors, such as inattentiveness (Durmer & Dinges, 2005), risk-taking (Killgore, 2007), and relapse in substance abusers (Gillin, 1998).

3. For a review of neural networks involved in emotion regulation, see Ochsner and Gross (2005).

Shared Neurobiological Substrates of Sleep and Addictions

Neurobiologically, both animal models and human neuroimaging studies demonstrate common substrates for sleep regulation and addictions. First, the hypocretin/orexin system, which is central for sleep–wake regulation, has also been implicated in the development of drug-seeking behaviors to various substances including opiates, alcohol, and nicotine and stimulation of hypocretin neurons was sufficient to reinstate extinguished place preference paired with morphine, and extinguished alcohol or nicotine seeking behaviors. Further, hypocretin receptor antagonists have been found to reduce self-administration of alcohol, nicotine, or opiates (Hoyer & Jacobson, 2013; Tsujino & Sakurai, 2009).

Second, although, unlike other midbrain monoaminergic nuclei (raphe and locus ceruleus), firing rates of neurons in the SN and VTA do not vary with arousal states, these nuclei share direct bidirectional connections with brain regions involved in sleep regulation, including the raphe and locus ceruleus, cholinergic cells in the midbrain and basal forebrain, neurons that modulate behavioral state in the thalamus, and hypocretin neurons in the hypothalamus (Monti & Monti, 2007). Consistently, stimulation of postsynaptic dopamine receptors in the NAcc, and other striatal regions, increases arousal and delays sleep (Barik & de Beaurepaire, 2005).

Importantly, recent studies suggest that synaptic dopamine is associated with mechanisms of sleep homeostasis. In one study, fruit flies carrying the *Dat*^{lo} mutation, which reduces enzymatic clearance of dopamine, displayed a greater sleep rebound after sleep deprivation than did wild-type controls (Greenspan, Tononi, Cirelli, & Shaw, 2001). Similarly, Holst et al. (2014) found that human homozygotic carriers of an allele of the dopamine transporter that reduces dopamine transporter availability (*10R/10R*, Costa, Riedel, Müller, Möller, & Ettinger, 2011) had a greater SWA rebound after sleep deprivation. It is yet to be determined whether this SWA rebound is associated with the downregulation of D2/D3 receptors (Volkow et al., 2012). However, as increased synaptic dopamine in the striatum induces the homeostatic SWA response, consistent with the notion that excess dopamine in this region results in synaptic scaling (Thomas et al., 2008), potentially postdrug administration SWS is involved in the strengthening of behavioral patterns associated with the drug.

SLEEP, PLASTICITY, AND ADDICTIONS—TYING IT ALL TOGETHER

I would like to conclude with several key assertions based on the mechanistic links discussed here:

1. If excess dopamine during wake induces increased SWA during sleep, a similar effect can be proposed for hedonic effects of drug exposure. This homeostatically induced SWA may then strengthen associative learning linking environmental cues with drug use behaviors, in accordance with the synaptic homeostasis hypothesis. Partial support for this conjecture comes from a study by Lansink, Goltstein, Lankelma, McNaughton, and Pennartz (2009), who found that neuronal activity in the ventral striatum and hippocampus of rodents while learning reward-related spatial task, was spontaneously reactivated during SWS.
2. Sleep disruption downregulates dopamine receptors in the NAcc (Volkow et al., 2012), which in turn may "jump-start" plastic changes in the mesolimbic dopaminergic system associated with the transition from recreational drug use to drug dependence. This is consistent with findings showing less activation in the ventral striatum, during reward anticipation, associated with more chronically disturbed sleep (Holm et al., 2009).
3. REM sleep may reinforce emotional learning such as reduction of NA via drug self-administration. This is consistent with studies demonstrating increased bursting activity in the NAcc and VTA during REM sleep (Dahan et al., 2007; Lena et al., 2005) and the fact that the extent of emotional memory consolidation is associated with specific REM sleep characteristics (reviewed in Walker & van der Helm, 2009).

Putting it all together, converging neurophysiological, neuroimaging, and clinical findings suggest that reward systems are reactivated during sleep, leading to the argument that sleep is important for offline consolidation of memories with elevated emotional or motivational value, which in turn enhance learning and synaptic plasticity of addiction-related behaviors. Additionally, whether due to a prior disposition for insomnia or sleep disturbances incurred by the use of the drug, the chronic sleep debt would cause (1) a greater sensitivity to drug cues, (2) greater REM sleep rebound, which would enhance emotional learning, and (3) SWA, which would enhance neuroplastic adaptive changes in the striatum.

Thus, a hypothetical model can be derived combining these findings:

1. Chronically disrupted sleep causes NA states, which may increase drug-seeking behaviors, or reinstatement due to exposure to cues.
2. Chronically disrupted sleep also disrupts mesolimbic dopaminergic signaling, which may accelerate neural adaptation associated with repeated drug exposure.
3. REM and NREM sleep may each contribute to the consolidation of learning associated with drug reinforcement.
4. Finally, the consumption of the drug may, in and of itself, disrupt sleep, by increasing arousal and disrupting the alignment of circadian and homeostatic processes (Figure 37.2).

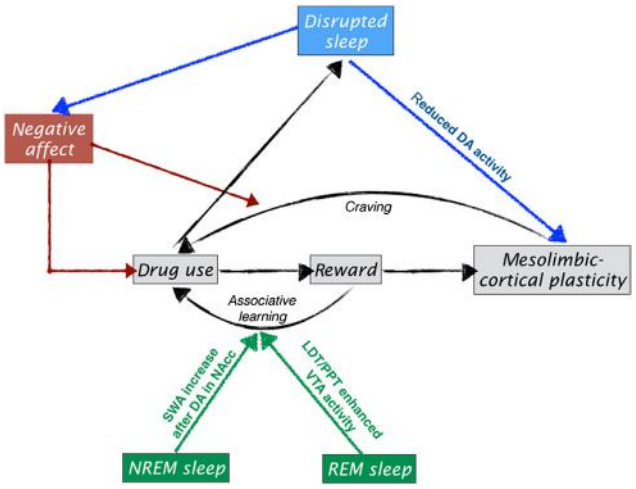

FIGURE 37.2 Proposed model linking sleep mechanisms with addictions. A hypothetical model for the role of sleep and sleep difficulty in addictions: (A) Chronically disrupted sleep causes NA and negative mood, which may increase drug-seeking behaviors, or reinstate previous drug use when exposed to cues. (B) Disrupted sleep also disrupts mesolimbic dopaminergic signaling, which may accelerate neural adaptation associated with repeated drug exposure. (C) Both REM and NREM sleep contribute to the consolidation of learning associated with drug reinforcement. (D) Finally, the consumption of the drug may, in and of itself, disrupt sleep, by increasing arousal and disrupting the alignment of circadian and homeostatic processes. NA, negative affect; REM, rapid eye movement; NREM, non-rapid eye movement.

CONCLUDING REMARKS

This model brings us back to the opening question of this chapter, why don't we sleep more? Further, the fact the mesolimbic dopamine activity is increased during REM would suggest that sleep may be rewarding in and of itself. Potentially sleeping, or at least REM sleeping, is a reinforcing experience, although this hasn't been tested empirically. Will a sleep-deprived rat be willing to work to catch a few zzz's? Arguably, in order to experience the hedonic effects of sleep we need to be sleep deprived. If this is indeed the case, our tendency to maintain a degree of sleep deprivation is itself a form of addiction, and we are in fact "addicted" to increased durations of arousal in the same way as some individuals are "addicted" to risky behaviors or exercise. A tendency to prolong our waking hours, to enjoy the ensuing sleep, is perhaps another BAS behavior indicative of risk. These are all hypotheses that should be addressed empirically, and hopefully will expand our understanding of sleep function.

In sum, we have seen that sleep disturbances may disrupt mood regulation, and increase approach tendencies, thereby increasing the risk that individuals will attempt to alleviate their negative emotions by self-medication, and/or also experience greater reinforcing effects after drug use. Sleep patterns, even disrupted sleep, may contribute to the consolidation of cue-induced drug seeking behaviors, and other adaptive changes associated with the development of addictions.

Both addictions and sleep regulation are highly complex global systems that encapsulate everything from higher cognitive functions such as emotion regulation, through motor patterns, to intracellular metabolic processes. Capturing this complexity is beyond the purview of a single chapter, but I attempted here to grab several threads from the two disciplines and tie them together, laying the foundation for a novel mechanistic model linking the two.

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Chapter 38

Alcohol and Sleep-Disordered Breathing

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INTRODUCTION

Alcohol consumption is associated with elevated morning blood pressure levels (Ohira et al., 2009) and increased mortality from cardiovascular disease (Ikehara et al., 2008). Experimental studies report that alcohol consumption relaxes upper airway dilator muscles, increases upper airway resistance, may induce sleep-disordered breathing (SDB) (Mitler, Dawson, Henriksen, Sobers, & Bloom, 1998), and increases the duration (Berry, Bonnet, & Light, 1992) and frequency (Scanlan, Roebuck, Little, Redman, & Naughton, 2000) of occlusive episodes in patients with SDB. Several patient-based studies report that patients who snore or have SDB who consume alcohol prior to bedtime have an increased number and duration of hypopneic and apneic episodes (Scanlan et al., 2000; Taasan, Block, Boysen, & Wynne, 1981; Tsutsumi, Miyazaki, Itasaka, & Togawa, 2000) and require higher levels of continuous positive airway pressure (CPAP) to prevent apnea and hypopnea (Mitler et al., 1998).

In contrast, though several community-based studies report that alcohol consumption is positively associated with snoring in men (Enright et al., 1996; Jennum, Hein, Suadicani, & Gyntelberg, 1992), and in combined male and female populations (Jennum & Sjol, 1993), not all studies have found an association (Olson, King, Hensley, & Saunders, 1995; Schmidt-Nowara, Coultas, Wiggins, Skipper, & Samet, 1990). Furthermore, an association between alcohol consumption and SDB is displayed in men (Peppard, Austin, & Brown, 2007; Sakurai, Cui, Tanigawa, Yamagishi, & Iso, 2007; Stradling & Crosby, 1991; Tanigawa et al., 2004) and in Japanese women (Cui et al., 2011), but not in American women (Peppard et al., 2007) (Table 1). However, Japanese community-based studies report that the association between alcohol consumption and SDB is more evident in both male and female subjects with a low body mass index (BMI) compared to those with a high BMI (Cui et al., 2011; Tanigawa et al., 2004).

This investigation's review of existing literature shows that research is largely supportive of an association between alcohol consumption and SDB in adult men and women and a synergistic action between BMI and alcohol consumption on SDB.

PATIENT-BASED STUDIES

An experimental study of 20 asymptomatic male volunteers reported that alcohol consumption at night (2 mL/kg body weight) was associated with an increase in episodes of arterial oxygen desaturation (from 118–226, $p<0.01$) and the number of apneic episodes per night (from 20–110, $p<0.01$) (Taasan et al., 1981) compared with placebo. In a study of 21 habitually snoring men aged 30–60 years, alcohol consumption prior to bedtime (0.5 g/kg body weight) was associated with an increase in the apnea–hypopnea index (AHI) on alcohol nights (9.7 ± 2.1/h) compared with control nights (7.1 ± 1.9/h) ($p=0.02$) (Scanlan et al., 2000). Additionally, a study of 37 male patients (mean age = 46.9 years) with SDB showed higher mean 3% oxygen desaturation indexes (ODI) after alcohol intake (15.9/h) compared with control conditions (12.7/h) ($p=0.01$) (Tsutsumi et al., 2000). Alcohol consumption prior to bedtime in patients who snore necessitates a higher level of CPAP to prevent apnea and hypopnea compared with controls. A study of six men aged 33–70 years found that the CPAP required to eliminate snoring was 4.8 ± 1.7 cm H_2O on placebo nights and 6.2 ± 1.5 cm H_2O on alcohol consumption nights ($p=0.05$) (Mitler et al., 1998).

Modulation of Sleep by Obesity, Diabetes, Age, and Diet. http://dx.doi.org/10.1016/B978-0-12-420168-2.00038-7

TABLE 1 Alcohol Consumption and Sleep-Desordered Breathing

Author/Year	Country	Subjects	Alcohol Consumption	Endpoint	
				SDB	Mean or OR
Patient-Based Study					
Scanlan et al. (2000)	Australia	21 men and women aged 30–60 years	0.5 g/kg of body weight, alcohol night vs placebo night	Mean AHI	9.7/h vs 7.1/h, $p=0.02$
Taasan et al. (1981)	United States	20 men, mean age 48.3 years	2 ml/kg of body weight, alcohol night vs placebo night	Number of apneic events per night	20 vs 110, $p<0.01$
Tsutsumi et al. (2000)	Japan	37 men, mean age 46.9 years	After alcohol consumption vs control	Mean 3% ODI	15.9/h vs 12.7/h, $p=0.01$
Population-Based Study					
Jennum et al. (1992)	Denmark	3323 men and women aged 54–74 years	<290 g/week vs ≥290 g/week	Snoring	1.19 (1.10–1.29)
Olson et al. (1995)	United States	441men and women aged 34–69 years	10 g/d increase in current alcohol consumption	Snoring	1.05 (0.84–1.31)
Schmidt-Nowara et al. (1990)	United States	1206 men and women aged ≥18 years	Nondrinkers vs ≥6 drinks/week	Snoring	0.8 (0.5–1.5)
Cui et al. (2011)	Japan	3113 women aged 30–69 years	Never drinkers vs current ethanol intake ≥23 g/day	Snoring 3% ODI ≥5	3.0 (1.1–5.8) 1.8 (1.0–3.4)
Tanigawa et al. (2004)	Japan	1425 men aged 40–69 years	Never drinkers vs current ethanol intake ≥1.0 g/day per kg	3% ODI ≥5	1.95 (1.15–3.31)
Peppard et al. (2007)	United States	775 men and 645 women aged 30–60 years	Increment of 1 alcohol drink per day	AHI >5	Men: 1.25 (1.07–1.46), women: 0.94 (0.67–1.33)
Sakurai et al. (2007)	Japan	1465 men aged 20–69 years	Nondrinkers vs current ethanol intake ≥1.0 g/day per kg	3% ODI ≥5	3.4 (2.1–5.6)

OR, odds ratio; SDB, sleep-disordered breathing; AHI, apnea–hypopnea index; 3% ODI, 3% oxygen desaturation index.

POPULATION-BASED STUDIES

Several previous studies using snoring to estimate SDB reported that alcohol consumption is positively associated with the prevalence of SDB (Enright et al., 1996; Jennum et al., 1992; Jennum & Sjol, 1993); however, not all studies have found this association (Olson et al., 1995; Schmidt-Nowara et al., 1990). The Cardiovascular Health Study reported that snoring was positively associated with alcohol use in men, but not women, among 5201 subjects aged 65 and older (Enright et al., 1996). The Copenhagen Male Study of 3323 men aged 54–74 years reported that snoring was more prevalent among men who consume ≥290 g/week of alcohol compared with men who consume <290 g/week, with an odds ratio (OR) and 95% confidence interval of 1.19 (1.10–1.29) (Jennum et al., 1992). The MONICA II Study reported that snoring and a respiratory distress index of ≥5/h were positively associated with alcohol intake among 1504 men and women aged 30, 40, 50, and 60 years ($p<0.05$) (Jennum & Sjol, 1993). An Australian community-based study reported that alcohol consumption was not associated with snoring among 2202 men and women aged 33–69 years, with an OR of 1.05 (0.84–1.31) for an increase in current alcohol consumption of 10 g/day (Olson et al., 1995). Additionally, a study of 1206 American men and women aged 18 years and older also reported that consumption of six or more alcoholic drinks per week did not impact on snoring in a comparison with nondrinkers, with an OR of 0.8 (0.5–1.5) (Schmidt-Nowara et al., 1990).

The association between alcohol consumption and SDB has been shown in men (Peppard et al., 2007; Sakurai et al., 2007; Stradling & Crosby, 1991; Tanigawa et al., 2004) and in Japanese women (Cui et al., 2011), but not in American women (Peppard et al., 2007). Based on estimations of SDB using 4% ODI of >5, a European community-based study of 893 men aged 35–65 years reported that alcohol consumption was positively associated with SDB ($r=0.2$, $p<0.001$) (Stradling & Crosby, 1991). The Wisconsin Sleep Cohort Study of 775 men and 645 women aged 30–60 years reported that an AHI of >5 was more prevalent among male subjects who consumed three alcoholic drinks/day compared with nondrinkers, but was not different among female subjects; the multivariable OR was 1.94 (1.21–3.09), p for trend = 0.006, for men; and 0.83 (0.30–2.33), p for trend = 0.73, for women (Peppard et al., 2007). A Japanese community-based study of 1425 men aged 40–69 years reported that the prevalence of 3% ODI of ≥5 was higher among subjects who consumed ≥1.0 g/day per kg body weight of alcohol compared with nondrinkers, with a multivariable OR of 1.95 (1.15–3.31), p for trend <0.01 (Tanigawa et al., 2004). Another study of professional Japanese male truck drivers aged 20–69 years reported that the prevalence of 3% ODI of ≥5 was higher among subjects who consumed ≥1.0 g/day per kg body weight compared with nondrinkers, with a multivariable OR of 3.4 (2.1–5.6) (Sakurai et al., 2007). A later community-based study of 3113 Japanese women aged 30–69 years reported that the prevalence of 3% ODI of ≥5 was higher among women who consume ≥23 g/day of alcohol compared with nondrinkers: the multivariable OR was 3.0 (1.6–5.8) for snoring, and 1.8 (1.0–3.4) for 3% ODI ≥5 (Cui et al., 2011).

ALCOHOL CONSUMPTION AND SDB BY BMI SUBGROUPS

Limited research has examined the association between alcohol consumption and SDB with analysis stratified by BMI subgroups (Cui et al., 2011; Sakurai et al., 2007; Tanigawa et al., 2004). Studies show that the association between alcohol consumption and SDB is more evident in subjects with a lower median BMI than in those with a higher median BMI, although this interaction is not statistically significant (Cui et al., 2011; Sakurai et al., 2007; Tanigawa et al., 2004). A study of 1425 men aged 40–69 years found a multivariable OR of 2.31 (1.13–4.72) for BMI <23.9 kg/m^2, and 1.13 (0.52–2.44) for BMI ≥23.9 kg/m^2 (Tanigawa et al., 2004). A study of 1425 men aged 20–69 years found a multivariable OR of 11.4 (3.2–41) for BMI <23.4 kg/m^2, and 1.2 (0.6–2.7) for BMI ≥23.9 kg/m^2, p for interaction = 0.18 (Sakurai et al., 2007). A study of 3113 women aged 30–69 years found a multivariable OR of 2.7 (1.0–6.7) for BMI <23.0 kg/m^2, and 1.5 (0.6–3.3) for BMI ≥23.0 kg/m^2, p for interaction = 0.23 (Cui et al., 2011). The Wisconsin Sleep Cohort Study (Peppard et al., 2007) of 645 women aged 30–60 years found no association between alcohol consumption and SDB in women consuming three drinks/day compared with nondrinkers, with a multivariable OR of 0.83 (0.30–2.33), p for trend = 0.73. However, although the mean BMI of subjects in this study (31 kg/m^2) was much higher than in Japanese women (23 kg/m^2), this study did not conduct further analysis with stratification for BMI subgroups (Cui et al., 2011). BMI is a major risk factor for SDB, suggesting that the strong effect of excess weight on SDB may mask a moderate effect of alcohol consumption (Schmidt-Nowara et al., 1990). In addition, positional sleep apnea occurs more commonly in less obese subjects (Oksenberg, Silverberg, Arons, & Radwan, 1997). Furthermore, Asian subjects tend to have a more inferiorly positioned hyoid bone and a narrower posterior airway space compared with Caucasians (Villaneuva, Buchanan, Yee, & Grunstein, 2005).

CONCLUSION

Habitual alcohol consumption is associated with a higher prevalence of snoring and SDB among adult men and women.

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Chapter 39

Patterns of Alcohol Consumption and Sleep in Shiftworkers

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SHIFTWORK, SLEEP, AND HEALTH

Due to demand for round-the-clock services and production, a growing proportion of the workforce is engaged in nonstandard hours—outside the traditional 9 am–5 pm, Monday–Friday work week. Often referred to collectively as shiftwork (Härmä, 1998), such schedules involve long and irregular hours, frequently including combinations of early morning, evening, and night shifts. The prevalence of shiftwork has been estimated at approximately 20% in urban economies (Rajaratnam & Arendt, 2001). Shiftwork disrupts our naturally diurnal circadian rhythms, such that shiftworkers (particularly on night shift) must work while biologically primed for sleep and sleep while primed for wake. This results in sleep of reduced quantity and quality compared to those on standard schedules (Åkerstedt, 2003; Rajaratnam & Arendt, 2001).

The gold standard for measuring sleep is polysomnography, which involves interpreting signal patterns from electrodes on the head to measure brain electrical activity (electroencephalogram), near the eyes to measure eye movement (electro-oculogram), and on the chin to measure muscle tone (electromyogram). These signals are measured across a sleep period, and 30 s blocks are visually scored according to standard criteria (Rechtschaffen & Kales, 1968). Sleep is categorized into stages: wake; wake–sleep transition (stage 1); light sleep (stage 2); deep, or slow-wave, sleep (stages 3 and 4); and rapid eye movement (REM) sleep. We refer to the staging of sleep across a period as sleep architecture (Carskadon & Dement, 2000). Not only is sleep time frequently reduced for shiftworkers, but sleep architecture is also disrupted (Åkerstedt, 2003).

Due to these disruptions in circadian rhythms and sleep, shiftwork is associated with elevated sleepiness, lowered mood, social and family disturbance, impaired performance, and increased safety risk (Rajaratnam & Arendt, 2001). There is also evidence that shiftworkers are more likely to develop cardiovascular and gastrointestinal problems (Åkerstedt & Knutsson, 1997; Lowden, Moreno, Holmback, Lennernas, & Tucker, 2010), metabolic issues including glucose intolerance (Schmid et al., 2011; Spiegel, Leproult, & Van Cauter, 1999), elevated cortisol levels (Reynolds et al., 2012; Spiegel et al., 2004) and obesity (Lowden et al., 2010), and certain types of cancer (Davis & Mirick, 2006).

Researchers working to understand the mechanisms behind health risks for shiftworkers have focused on physiological and behavioral factors. Physiological factors include sleep loss, circadian disruption, inadequate recovery time, and changes in light exposure and hormone production (Davis & Mirick, 2006). Behavioral factors include reduced exercise levels and changes to diet. For example, shiftworkers may be working during times of high social value, such as weekends and evenings, which can result in reduced participation in organized exercise, such as community sport (Atkinson, Fullick, Grindey, & Maclaren, 2008). Dietary changes that may contribute to poor health

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include altered timing of meals, such that the body is processing food at nonoptimal times in the natural circadian cycle (Waterhouse, Buckley, Edwards, & Reilly, 2003); changes in appetite and satiety (Suwazono et al., 2008); and eating foods that are quick and convenient due to reduced time for meals or eating outside typical times (Persson & Mårtensson, 2006; Waterhouse et al., 2003). It has also been suggested that shiftworkers may experience cravings for foods that are high in fats or sugars (Persson & Mårtensson, 2006), reflecting a compensatory strategy to combat the increased sleepiness arising from their work schedules.

Indeed, shiftworkers may use an array of strategies to compensate for elevated sleepiness, including consumption of stimulants, such as caffeine and nicotine (Knauth & Hornberger, 2003; Richardson, Miner, & Czeisler, 1989). Further, since they are often sleeping at biologically difficult times, shiftworkers may use sedatives to promote sleep, particularly when stress at work makes it difficult to wind down (Dorrian et al., 2011). Common sedatives include prescription medication and alcohol (Dorrian et al., 2011; Gold et al., 1992; Knauth & Hornberger, 2003; Richardson et al., 1989).

Although alcohol has sedative properties and often reduces the time taken to fall asleep (Ebrahim, Shapiro, Williams, & Fenwick, 2013; Roehrs & Roth, 2001), alcohol disrupts normal sleep architecture. The negative effects of alcohol on the body, particularly at high doses, are wide-ranging (Anderson, Chisholm, & Fuhr, 2009; Carr, 2011; Rehm et al., 2009; Room, Babor, & Rehm, 2005; Schuckit & Smith, 2006). Therefore, alcohol use among shiftworkers is likely to be putting extra pressure on already vulnerable physiological systems. This perceived compensatory mechanism for facilitating sleep may actually be exacerbating sleep loss, as well as further increasing health and safety risk. This chapter will describe the way that the body processes alcohol, the negative impact on the brain and liver, and the effects of alcohol on sleep. We will then examine the evidence surrounding patterns of alcohol use in shiftworkers, before turning to consideration of the potential effects of these patterns.

ALCOHOL AND HEALTH

Ethanol (C_2H_5OH) is an intoxicating, energy-yielding molecule produced by alcoholic fermentation from plants with high carbohydrate content (e.g., barley, wheat, corn, and grapes). The principal sources of dietary ethanol are beer, distilled spirits, and wine. Although ethanol provides calories, it is not considered an essential nutrient. Alcohol consumption is initially accompanied by alterations in memory, decreased attention, changes in mood, and drowsiness and production of mild euphoria (Valenzuela, 1997). Alcohol changes the balance in neurotransmitter action by increasing inhibitory and decreasing excitatory neurotransmission (or a combination of both). This explains the depressant or sedative action of alcohol (Table 1). Standard drinks are the main units for quantifying alcohol content across different container sizes and alcohol types. Standard drink definitions vary across countries, from the equivalent of 8 g of ethanol in the United Kingdom (UK) (Turner, 1990) to 10 g in Australia (NHMRC, 2009, pp. 1–179), 15 g in the United States (Ferreira & Weems, 2008), and 23.5 g in Japan (Turner, 1990).

Alcohol processing in the body occurs mainly in the gut and the liver. First-pass metabolism refers to the initial interaction of alcohol with the enzyme alcohol dehydrogenase (ADH) in the gut, where it begins to break down. Remaining alcohol diffuses across the stomach and proximal intestine to enter the bloodstream, which carries it to the liver, where there are two processing pathways. In the first, hepatic ADH breaks down the alcohol to form acetaldehyde. The detoxification rate of ethanol is limited by hepatic ADH, which can process alcohol at approximately 10–15 g/h (Goodsell, 2006), but this rate is influenced by body size, gender, drinking experience, food intake, and general health. Females produce less ADH compared to

TABLE 1 Spectrum of Negative Consequences Associated with Drinking at Risky Levels

Physical Damage, Disease	Family/Social Effects
• Brain • Endocrine system • Immune system • Vitamin and nutrient absorption • Dehydration • Blood thinning • Cancers (mouth, oropharynx, esophageal, liver, breast) • Epilepsy • Cardiovascular disorders (heart disease, stroke) • Gastrointestinal disease • Cirrhosis of the liver • Diabetes mellitus • Wernike's encephalopathy • Infection	• Family deprivation • Unintentional injury • Interpersonal violence • Injury/fatality caused through drunk driving • Reduced job performance • Absenteeism • Spread of sexually transmitted disease • Maternal and perinatal disorders • Judgments/negative attitude from others
Cognitive/Psychological Effects	**Safety Risk**
• Mild euphoria • Sedation • Frontal lobe dysfunction • Unipolar depressive disorders • Suicidal ideation • Anxiety • Korsakoff psychosis • Confusion • Hallucinations • Coma	• Motor vehicle accident • Falls • Drowning • Poisoning • Trauma • Burns • Death

Summary from reviews Room et al. (2005), Schuckit and Smith (2006), Anderson et al. (2009), Rehm et al. (2009), and Carr (2011).

males, such that more alcohol is absorbed in women for the equivalent amount of alcohol consumed (Baraona et al., 2001). Acetaldehyde is then converted to acetate in the presence of another enzyme called acetaldehyde dehydrogenase. Acetaldehyde has damaging effects on the brain and other tissue, whereas acetate is further metabolized in the body to form an energy source (Lieber, 1997).

The second pathway involves the microsomal ethanol-oxidizing system (MEOS) (Lieber, 2004), in which the oxidation of ethanol to acetaldehyde and acetic acid also leads to generation of reactive oxygen species (ROS) (Mello, Ceni, Surrenti, & Galli, 2008). ROS production and oxidative stress in liver cells play a central role in the development of alcoholic liver disease (Wu & Cederbaum, 2003). A high blood alcohol concentration and repeated exposures stimulates enzymes within the MEOS system, resulting in more efficient metabolism of alcohol and, hence, tolerance to its effects (Lieber, 2004).

Chronic alcohol and its metabolites prevent the body from properly absorbing, digesting, and using essential nutrients, which can lead to malnutrition (Lieber, 2003). For example, impaired fat metabolism results in triglyceride accumulation in the liver; this can be seen after a single episode of heavy drinking but can be reversed through abstinence from alcohol. However, if high alcohol intakes are maintained and fat continues to be deposited in liver, liver cells will die, leading to fibrous scar tissue (Table 1). In advanced cases of liver damage (cirrhosis) the reversibility of this damage is lost (Beier & McClain, 2010). Although liver damage is of great concern with excessive alcohol consumption, there are a number of other damaging health effects.

Alcohol has detrimental effects on most organ systems; however, numerous studies have used a J-shaped or U-shaped curve to describe the relationship between alcohol intake versus total mortality and cardiovascular mortality, indicating that low levels of alcohol (suggesting an optimal consumption of 1–2 standard drinks) may provide some benefit to cardiovascular health. However, these studies are observational and epidemiological in nature, and most reviews warn of not prescribing alcohol for those who do not drink (Kloner & Rezkalla, 2007). The negative effects of drinking at elevated or risky levels are well established (Anderson et al., 2009; Carr, 2011; Rehm et al., 2009; Room et al., 2005; Schuckit & Smith, 2006). Alcohol results in physical damage and disease, cognitive and psychological damage, increases in risk, and disruption of family and social relationships (Table 1).

ALCOHOL AND SLEEP

Alcohol ingestion results in a series of changes to sleep across the night, and these are dependent on dose of alcohol, time gap between ingestion and the sleep period, and whether ingestion was acute or chronic, as well as individual differences in alcohol metabolism (due to gender, tolerance, etc.) (Baraona et al., 2001; Lieber, 2004; Vitiello, 1997). Alcohol doses are frequently categorized as low (0.15–0.49 mg/kg, 1–2 standard drinks), moderate (0.5–0.74 mg/kg, 2–4 standard drinks), or high (>0.74 mg/kg, >4 standard drinks) (Ebrahim et al., 2013). Since the liver processes alcohol at a rate of approximately 10–15 g/h (Goodsell, 2006), low doses of alcohol will take 1–5 h to clear the system, while high doses will likely take at least 5 h. This means that, even at low doses, if alcohol is taken close to bedtime (as would happen if it was being used as a sleep aid), it is likely that the body will be processing the alcohol during the sleep period. The effects on sleep may be different depending on whether alcohol is still being processed or has been completely discharged. For this reason, studies typically analyze the sleep period in two halves, and in particular, highlight the findings during the first half of the night, in addition to looking at the sleep period as a whole.

Alcohol consumption can influence sleep by altering the time required to fall asleep (sleep latency) and the amount of wake after sleep onset (WASO) and by disrupting the sequence and duration of sleep states (architecture). Studies with single administration of low to moderate doses of alcohol have found that sleep latency and WASO during the first half of the night are reduced. There is some suggestion that slow-wave sleep (SWS) may be increased during the first half of the night. The results for REM sleep are variable. Shorter-onset latency, more consolidated early sleep (reduced WASO), and increased SWS are also found in acute, high-dose studies. Latency to REM is also increased (Table 2, reviewed in Brower, 2001; Ebrahim et al., 2013; Roehrs & Roth, 2001; Vitiello, 1997).

In contrast to the research into acute effects, there are fewer studies investigating the impact of chronic alcohol consumption at low doses on sleep. This research has focused on REM sleep, showing a decrease in REM during the first half of the night (Ebrahim et al., 2013). Much of the chronic high-dose work has been done in individuals with alcohol dependence. These studies also indicate an increase in SWS across the night, and a concomitant delay in REM onset and decrease in REM percentage. During subsequent periods of abstinence, REM rebounds, and REM onset latency returns to habitual levels (Table 2, reviewed in Brower, 2001; Ebrahim et al., 2013; Roehrs & Roth, 2001; Vitiello, 1997). An interesting difference for those who regularly consume alcohol is that sleep onset latency is increased. This has been explained as a reflection of a build-up of tolerance to the sedative, but not necessarily the stimulant, effects of alcohol (Brower, 2001). There also appear to be relatively long-lasting changes in the body's mechanisms of sleep regulation, with sleep issues in those with addiction problems lasting for up to a year following cessation of drinking (Vitiello, 1997).

TABLE 2 Summary of Effects of Alcohol on Sleep at Different Doses

Time Course	Dose	1st half of night	Overall
Acute	low-mod	↓SOL ↓WASO ↕REM ↑SWS	↕REM% ↕ROL ↕SWS
	high	↓SOL ↓WASO ↓REM% ↑SWS	↓REM% ↑ROL ↑SWS
Chronic	low-mod	↓REM	
	high	↑SOL	↓REM% ↑ROL ↑SWS ↓TST

Mod, moderate; REM, rapid eye movement sleep; REM%, REM percentage of total sleep time; ROL, REM onset latency; SOL, sleep onset latency; SWS, slow-wave sleep; TST, total sleep time; WASO, wake after sleep onset. ↑ indicates an increase, ↓ indicates a decrease, and ↕ indicates variable findings. Brown text indicates findings that have been found in most, but not all, studies of that type.

Overall, these findings have led to the commonly held belief that the primary effect of alcohol on sleep is as a REM suppressant. In other words, while the body is processing alcohol during the first part of the sleep period, REM is inhibited. Once the alcohol has been completely discharged from the body, later in the night, there is a REM rebound (Roehrs & Roth, 2001). Other studies finding increases in light sleep and wake during the second half of the night have also attributed this to a rebound following complete processing of the alcohol in the body (Roehrs, Yoon, & Roth, 1991; Williams, MacLean, & Cairns, 1983). A recent comprehensive review argues that rather than being a ubiquitous effect of alcohol, REM suppression during the first part of the sleep period is seen only at high doses of alcohol. The authors suggest that a more consistent description of the influence of moderate to high doses of alcohol on sleep would be that it increases SWS, delays REM onset, and reduces the overall percentage of REM across the night (Ebrahim et al., 2013).

The important implications for shiftworkers are that in the short term, while alcohol may help to reduce the time taken to fall asleep, sustained use may result in a buildup of tolerance and an associated delay in sleep onset. Sleep may be more consolidated during the first part of the night, but is likely to be disrupted later in the sleep period. Sleep architecture (proportion and timing of SWS and REM) is altered by alcohol. Taken together, rather than acting as a sleep aid, alcohol is likely to reduce sleep quantity and quality, exacerbating problems with sleepiness for shiftworkers.

ALCOHOL AND SHIFTWORK

Review articles from the last 15 years examining shiftwork and health outcomes have concluded that there is not enough evidence to link shiftwork to an increase in alcohol consumption (Boggild & Knutsson, 1999; Nicholson & D'Auria, 1999; Puttonen, Härmä, & Hublin, 2010; Zhao & Turner, 2008). Indeed, the literature is mixed, and interpretation is complicated by different methods of measuring alcohol consumption as well as varying approaches for defining and classifying shiftwork. Table 3 summarizes 17 studies that present relevant data. Of these, four are population-based surveys, and the remainder have employed surveys (and two of these also included diaries) to examine workers in particular industries. Several suggestions emerge when these studies are considered together:

- *Shiftworkers report using alcohol as a sleep aid.* Evidence that using alcohol as a sleep aid may be a common practice in shiftwork is consistent across the four studies that address this in male and female shiftwork populations (Dorrian et al., 2011; Gold et al., 1992; Morikawa et al., 2013; Richardson et al., 1989).
- *Average alcohol use is not higher in shiftworkers than in dayworkers.* Several studies found no differences, or even reductions, in average consumption for shiftworkers (Dorrian & Skinner, 2012; Hermansson et al., 2003; Hiro, Kawakami, Tanaka, & Nakamura, 2007; Kivimäki, Kuisma, Virtanen, & Elovainio, 2001; Romon et al., 1992). However, this does not mean that shiftwork has no effect on alcohol consumption. Rather, there may be differences in drinking *patterns* that are not reflected in

TABLE 3 Studies Investigating Shiftwork and Alcohol Consumption ($n = 16$)

Author (Date)	Participants	Occupation, Country	Male%	Methods	Findings
Population-Level					
Joyce et al. (2013)	FIFO = 380; SW = 913; other = 613	Employed, Australia	FIFO = 89% SW = 66% Other = 54%	Survey (phone)	• Mean drinks: FIFO = 4.2 drinks, SW and other = 3.4 drinks • Drinking days: FIFO = 3, SW = 2, other = 2.3 days
Dorrian and Skinner (2012)	$n = 2090$	Employed, Australia	SW = 62% DW = 54%	Survey (phone)	• SW sig ↑ odds drinking at risky levels (SW = 13%, DW = 10%) • SW sig ↓ odds drinking daily or near daily (SW = 13.5%, DW = 21%)
Thomas and Power (2010)	$n = 7839$	Employed, Britain	53%	Survey	• Drinks most days sig ↑ for evening and weekend work (≥1/week), but not nights or mornings
Gordon et al. (1986)	$n = 2436$	Employed, USA	50% variable SW = 75%	Survey (phone)	• % Heavy drinking (>4 drinks/day) ↑ in variable SW: males; variable SW = 16%, nonvariable SW = 11%; females; variable SW = 8%, nonvariable SW = 3%
Industry-Level					
Morikawa et al. (2013)	DW = 530 SW no nights = 72 SW with nights = 290	Light metal workers, Japan	100%	Survey	• 10% heavy drinking (≥60 g/day) • 24% used alcohol as a sleep aid: 29% in night SW compared to 22% DW and 13% SW who did not work at night • No sig group differences in median alcohol intake (≈13 g/day) • Sig ↑ odds of heavy drinking among night SW with ↓ sleep quality compared to DW who slept well
Dorrian et al. (2011)	Nurses = 41 Midwives = 21 Rotating shifts Nine males	Hospital nurses, Australia	14%	Survey and diary	• 44% reported using alcohol as a sleep aid • Sig ↑ odds of sleep aid use on workdays compared to days off, and with ↑ stress
Bushnell et al. (2010)	$n = 26,442$	Chemical manufacturer, multinational	69%	Survey	• Relative to 8 h DW, 12 h rotating SW had sig ↑ rate of heavy drinking; sig ↓ rate for 12 h DW, 12 h night, 8 h rotating, and 10 h rotating
Hiro et al. (2007)	$n = 17,501$	Nine companies and factories, Japan	100%	Survey	• No sig correlation between heavy drinking and SW
Hermansson et al. (2003)	DW = 319 2-SW = 294 3-SW = 297	Transport workers, Sweden		Alcohol screening tools	• 20% screened positive on AUDIT or serum alcohol biomarker (CDT) • Sig ↓ 2-SW screened +ve with CDT • No sig group differences in overall screening
Kivimäki et al. (2001)	SW = 506 DW = 183	Hospital nurses, Finland	0%		• No sig group differences in alcohol consumption
Härmä et al. (1998)	$n = 3020$	Postal, railway, industrial workers	100%	Survey	• Binary alcohol variable (cut-off = 0.25 L/year), low versus moderate/heavy users • % Heavy alcohol use ↑ in night work: DW = 53%; 2-SW = 55%; 3-SW = 50%; irregular SW = 50%; night SW = 69% • Alcohol use predicted sleep complaints

Continued

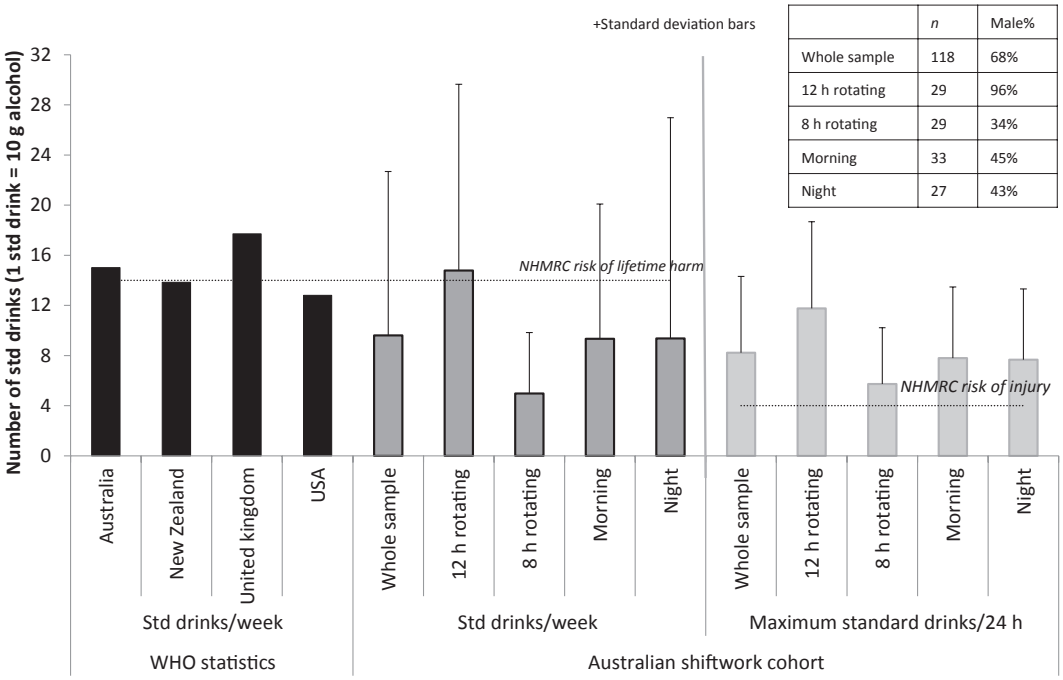
TABLE 3 Studies Investigating Shiftwork and Alcohol Consumption ($n = 16$)—cont'd

Author (Date)	Participants	Occupation, Country	Male%	Methods	Findings
Trinkoff and Storr (1998)	$n = 3917$	Nurses, USA	5%	Survey	• ↑ Crude% in alcohol use (≥5 drinks one occasion) for rotating (22%) and nightworkers (19%) compared to day and evening (16%) • Biggest risk of alcohol use in those working rotating or night shifts ≥8 h
Nakamura et al. (1997)	3-SW = 33 2-SW = 27 DW = 239	Blue-collar workers, Japan	100%	Survey	• % Drinking alcohol every day higher for 3-SW = 54% (morning/afternoon/night) than for 2-SW (days/nights) and DW (40%)
Lasfargues et al. (1996)	Night SW = 1200 DW = 1200	Workers, France	56%	Survey	• Alcohol ↓ in female night SW, no differences for males
Gold et al. (1992)	$n = 635$	Hospital nurses, USA	0%	Survey	• % Reporting alcohol as a sleep aid: DW/evening shifts = 27%; DW/evening + night shifts = 35%; night shifts = 25%; rotating shifts = 35% • ↑ Alcohol as a sleep aid in those who worked different shift types
Romon et al. (1992)	SW = 73 DW = 73	Chemical plant, nuclear station, France	100%	3-day record	• Sig ↓ alcohol in SW: SW = 9.3 g/day; DW = 15.6 g/day
Richardson et al. (1989)	Rotating SW = 171 DW = 27	Manufacturing plant, USA	–	Survey	• SW reported ↑ caffeine, ↑ alcohol • SW more likely to use alcohol as a sleep aid

AUDIT, alcohol use disorders identification test; CDT, carbohydrate-deficient transferrin test; SW, shiftworkers; DW, dayworkers; FIFO, fly-in/fly-out; ↑, increase; ↓, decrease; Sig, statistically significant ($p < 0.05$).

central tendency statistics. The variability in estimates for alcohol consumption in shiftworkers is large. This variability may result from gender and scheduling factors. These are discussed in the points that follow.

- *Gender likely plays a role*. As mentioned earlier, males have differential capability for processing alcohol compared to females (Baraona et al., 2001) and males consume higher amounts of alcohol (Bradley, Badrinath, Bush, Boyd-Wickizer, & Anawalt, 1998). Many of the studies investigating shiftwork and alcohol consumption may find patterns of consumption that reflect an overrepresentation of males or females in certain shiftworking groups. For example, Joyce, Tomlin, Somerford, and Weeramanthri (2013) found that Fly-In/Fly-Out (FIFO) shiftworkers were more likely to drink to excess. However, FIFO workers consisted of a higher proportion of males than other workers (Joyce et al., 2013). Indeed, many industry-level studies consisted mostly (Bushnell, Colombi, Caruso, & Tak, 2010) or entirely (Härmä, Tenkanen, Sjoblom, Alikoski, & Heinsalmi, 1998; Morikawa et al., 2013; Nakamura et al., 1997; Romon et al., 1992) of male participants. In contrast, studies in nursing have included nearly all female participants (Dorrian et al., 2011; Gold et al., 1992; Trinkoff & Storr, 1998). Certainly, one industry-level study with a unique roughly even gender distribution found differences in schedule effects on drinking for males compared to females (Lasfargues, Cacès, Le Clésíau, Lecomte, & Tichet, 1996).
- *Patterns of alcohol use are different for shiftworkers*. Rather than consistently drinking at elevated levels, shiftworkers may binge drink. A recent Australian population-based study found that, controlling for gender, age, job demands, having a child (<17 year), and work hour preference, shiftworkers had significantly reduced odds of drinking every (or nearly every) day, but increased odds of drinking to risky levels (Dorrian & Skinner, 2012). This study did not investigate differences between shift schedules. It may be that shiftworkers using alcohol as a sleep aid are only doing so after certain shifts, for example, just night shifts out of a rotation of nights, mornings, and afternoons (this



	n	Male%
Whole sample	118	68%
12 h rotating	29	96%
8 h rotating	29	34%
Morning	33	45%
Night	27	43%

FIGURE 1 Black bars display the average alcohol consumption per person per week in Australia, New Zealand, the UK, and the United States. *(Data are from the World Health Organisation (WHO) Global Status Report on Alcohol and Health, 2011.)* Recorded consumption in liters/year (LY) was converted to standard drinks per week (DW) (DW = (LY*789)/52/10, assuming 1 L alcohol = 0.789 kg, and 1 standard drink = 10 g). Gray bars (+standard deviation) standard drinks per week and maximum standard drinks in a 24 h period in a cohort of Australian shiftworkers. Table indicates sample size and %male participants. NHMRC, National Health and Medical Research Council.

type of shift rotation is common, e.g., Dorrian et al., 2011). Alternatively, since shiftwork schedules lead to reduced time off during periods of high social value (evenings, nights, weekends), it may be that opportunities to drink socially are reduced. When they do occur, shiftworkers may consume alcohol at elevated levels. Both alternatives could lead to alcohol consumption that is not consistent, but is clustered around certain times within a schedule.

- *Differences may result from type, length, and combination of shifts and the way in which these factors interact*. While some findings have suggested that shiftwork increased heavy drinking (Härmä et al., 1998), other studies have found that it was reduced among night shiftworkers (Bushnell et al., 2010). A British study found that while near-daily drinking was increased for workers on shift patterns that included weekends and evenings, it was not increased for those on night and morning shifts (Thomas & Power, 2010). Rather than a blanket effect of shift type, shift type may interact with other scheduling factors to influence alcohol consumption. For example, Morikawa et al. (2013) found that odds of heavy drinking were increased among night shiftworkers with poor sleep quality, compared to dayworkers who slept well. Other studies have suggested that it may be the combination of night work and long and rotating shifts (switching between nights and other shifts) that may be associated with less optimal patterns of alcohol consumption (Bushnell et al., 2010; Gold et al., 1992; Gordon, Cleary, Parker, & Czeisler, 1986; Nakamura et al., 1997; Trinkoff & Storr, 1998).

An illustrated example of these suggestions from Table 1 is displayed in Figure 1. In the black bars are an estimate of the number of standard drinks per week (in Australian standard drink units = 10 g alcohol) in Australia, New Zealand, the UK, and the United States (data from WHO, 2011). The gray bars show self-reported standard (std) drinks/week and maximum number of std drinks/24 h from a recent study conducted by our group in Australian shiftworkers ($n = 118$). In this study, shiftworkers (mean age ± SD = 43.4 ± 9.9 year, 68% male) completed a dietary questionnaire (Hodge, Patterson, Brown, Ireland, & Giles, 2000) on which they recorded frequency and amount of alcohol consumed over the preceding year. Superimposed on the figure are current Australian National Health and Medical Research Council (NHMRC) indicators of lifetime harm (>2 std drinks/day; ≥14 std drinks/week) and risk of injury (>4 std drinks in one session) (NHMRC, 2009, pp. 1–179). Consistent with the summary of findings from studies in Table 1, these data suggest that average alcohol consumption is not higher, and may actually be lower, among shiftworkers than in the

overall population in Australia (and other developed countries with similar, high levels of general alcohol consumption). There are apparent differences between schedules. In particular, the 8 h rotating schedule has a lower average consumption than the 12 h rotating schedule. These schedules represent those with the lowest and highest proportion of males, respectively. There are large standard deviation bars, reflecting large variability within each schedule. Further, while average consumption may be lower, average std drinks consumed in one sitting is higher for all schedules than recommended levels for risk of injury (NHMRC, 2009, pp. 1–179). This supports the suggestion that shiftworkers may binge drink.

While further research to tease out differences resulting from gender and from interactions between shift type and other scheduling factors (shift length, rotation) would be of benefit, overall (Table 1, Figure 1), research suggests that the patterns of alcohol consumption in shiftworkers may be harmful. This is further highlighted by studies investigating the influence of alcohol consumption for health and safety outcomes for shiftworkers, as described in the following, and final, section of this chapter.

Are Shiftworkers More Vulnerable to Alcohol's Negative Effects?

There is extensive literature on the negative impact of alcohol on health and safety. If we consider the primary pillars of health—sleep, diet, and exercise (Figure 2(A))—alcohol serves to undermine the foundations of healthy balance in the body. As discussed earlier, alcohol affects sleep architecture and, especially at higher doses, may result in sleep that is less consolidated, particularly later in the sleep period (Ebrahim et al., 2013; Roehrs et al., 1991; Williams

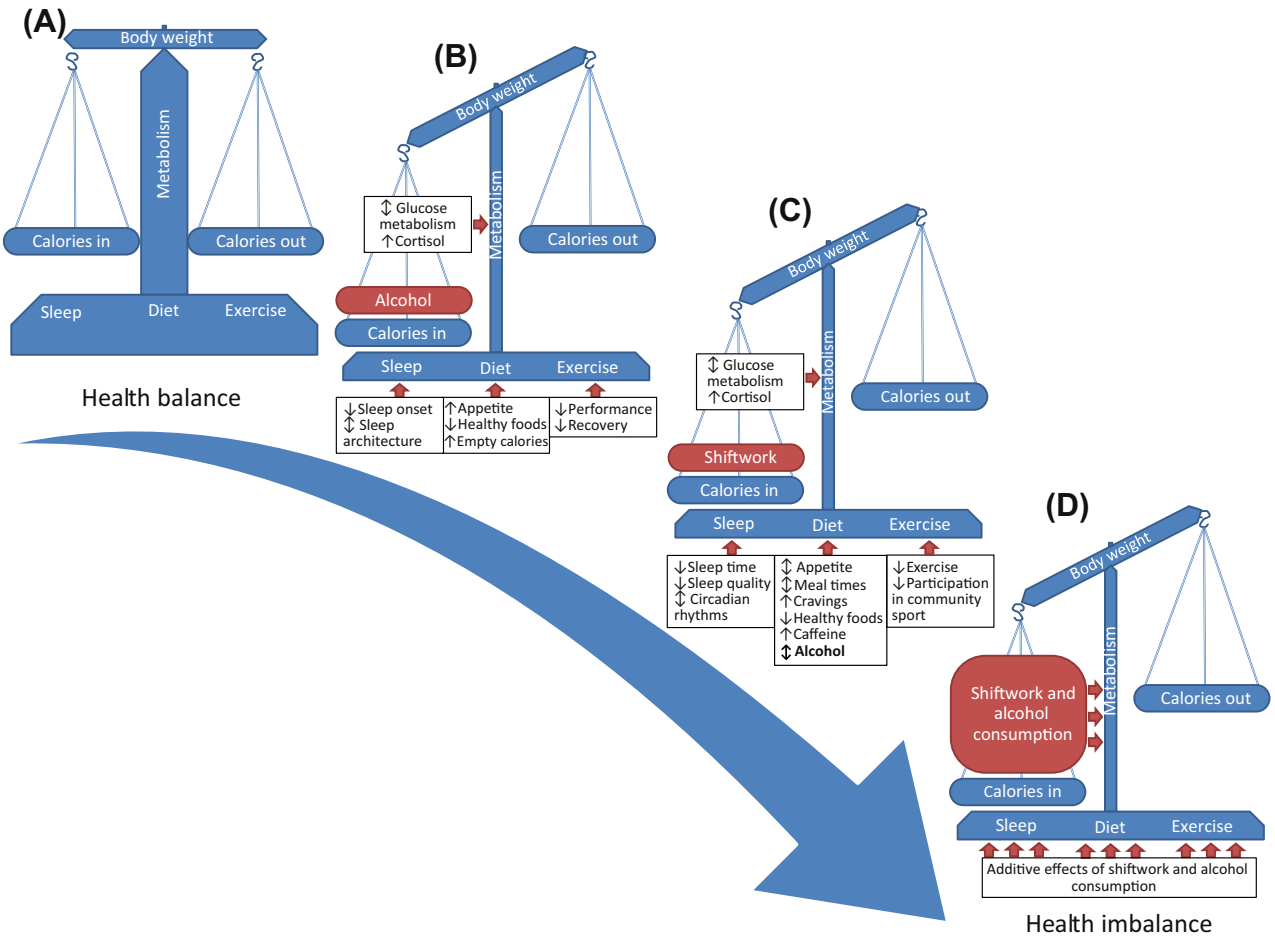


FIGURE 2 Suggested ways in which alcohol consumption and shiftwork contribute to behavioral and physiological changes that influence health. (A) Health balance - a strong foundation of healthy sleep, diet and exercise patterns support efficient metabolism, calories in match calories out and body weight is stable. (B) Alcohol consumption has a negative impact on sleep, diet, exercise and metabolism. (C) Shiftwork has a negative impact on sleep, diet, exercise and metabolism. (D) Health imbalance. Together, alcohol and shiftwork result in sleep loss, altered diet, and reduced energy expenditure, as well as metabolic impairment. Shiftworkers may be more likely to consume alcohol (especially as a sleep aid) and may also be more vulnerable to the negative effects of alcohol.

et al., 1983). Alcohol can stimulate appetite (Hetherington, Cameron, Wallis, & Pirie, 2001), as well as reward pathways, and is high in empty calories (no nutritional benefit), which can lead to unhealthy food selection (Breslow, Guenther, Juan, & Graubard, 2010). Alcohol negatively impacts on metabolism, elevating cortisol (Adinoff, Ruether, Krebaum, Iranmanesh, & Williams, 2003) and disrupting glucose control (Lieber, 2003). Alcohol can also negatively impact on exercise through impairment to muscle and cardiovascular function, which can limit performance and recovery (Vella & Cameron-Smith, 2010). Together, this results in health imbalance, where calories in outweigh calories out (Figure 2(B)). Sleep disturbance (Ebrahim et al., 2013), as well as changes in risk perception, risk taking, and motor impairment, lead to increased likelihood of accident and injury (Room, Babor, & Rehm, 2005).

Interestingly, the effects of alcohol and shiftwork on sleep, diet, and hormones are parallel in many ways (Figure 2(C)). Shiftwork also undermines health balance, with negative impacts on sleep, diet, and exercise (Atkinson et al., 2008; Waterhouse et al., 2003). Shiftwork is associated with reduced sleep quality and quantity and disruptions to biological rhythms (Åkerstedt, 2003; Rajaratnam & Arendt, 2001). There is increasing evidence that shiftwork changes mealtimes (Waterhouse et al., 2003), appetite (Suwazono et al., 2008), and cravings (Persson & Mårtensson, 2006), which may lead to unhealthy food selection. Due to their work hours, shiftworkers may participate in reduced exercise (Atkinson et al., 2008). Shiftwork may also impair metabolism through changes to glucose and cortisol (Reynolds et al., 2012; Schmid et al., 2011; Spiegel et al., 2004; Spiegel et al., 1999). For shiftworkers, reduced sleep and circadian disruption lead to increased likelihood of accident and injury (Rajaratnam & Arendt, 2001).

Given the similarities, it is reasonable to suggest that alcohol may exacerbate the negative impact of shiftwork on the health and safety of the worker (Figure 2(D)). Studies have suggested that the impairment produced by alcohol and sleep loss combined is greater than either effect in isolation (Banks, Catcheside, Lack, Grunstein, & McEvoy, 2004; Peeke, Callaway, Jones, Stone, & Doyle, 1980). Sleep-deprived shiftworkers may therefore be more vulnerable to the effects of alcohol. Field studies provide support for this idea. For example, Härmä et al. (1998) found that alcohol consumption resulted in impaired sleep and increased sleepiness in shiftworkers, but not dayworkers. Arnedt, Owens, Crouch, Stahl, and Carskadon (2005) found that alcohol exacerbated decrements in sleepiness and performance in medical residents. Gold et al. (1992) found that sleep aid use in nurses predicted accidents.

Taken together, research suggests that alcohol use among shiftworkers may be further tipping the balance toward negative health and safety impacts. While alcohol use may be perceived as a tool to recover some of the sleep deficits experienced by shiftworkers, it may be doing more harm than good. Additional research to examine some of the complexities of the relationship between shiftwork and alcohol consumption is both timely and important.

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Part VIII

Surgery

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Chapter 40

The Impact of Bariatric Surgery on Obstructive Sleep Apnea

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CURRENT STATE OF OBESITY

A significant increase in obesity is a major problem in developed countries, especially in the United States. The obesity rate in the United States has increased dramatically over the past 30 years after remaining relatively stable during the 1960–1980s (Flegal, Carroll, Kuczmarski, & Johnson, 1998). Obesity is defined as a body mass index (BMI) of >30 kg/m^2. Recent studies show that 35.7% of adults in the United States are obese (men 35.5%, women 35.8%), which is a significant increase from the early 1960s, when 13.4% (men 10.6%, women 16.2%) of adults were obese. The increase in obesity is more significant in adults, as those with a BMI > 40 currently comprise 5.7% (men 4.2%, women 7.2%) of the population while they were only 0.8% (men 0.3%, women 1.4%) in the 1960s. The obesity epidemic has affected other age groups, and presently about 16.9% of children and adolescents are obese (Flegal, Carroll, Kit, & Ogden, 2012; Flegal et al., 1998; Ogden, Carroll, Kit, & Flegal, 2013). This increase in obesity is associated with an increase in obesity-related diseases as well, especially type 2 diabetes, dyslipidemia, nonalcoholic fatty liver disease, cardiovascular disease, several types of cancer (endometrial, postmenopausal breast, kidney, and colon cancers), musculoskeletal disorders, gallbladder disease, and obstructive sleep apnea (OSA). These sequelae have led to a significant health burden, and it is estimated that obesity causes about 400,000 deaths per year in the United States alone and may soon overtake tobacco as the leading cause of death (Mokdad, Marks, Stroup, & Gerberding, 2004). Also, obesity is responsible for 5–7% of total annual medical expenditure in the United States and the total (direct and indirect) cost of obesity may now be as high as US$139 billion/year (Finkelstein, Ruhm, & Kosa, 2005).

OBSTRUCTIVE SLEEP APNEA: DEFINITION AND CLINICAL FEATURES

Obstructive sleep apnea, also called obstructive sleep apnea syndrome (OSAS), is the most common form of sleep-related breathing disorders. The term sleep-related breathing disorder, or sleep-disordered breathing, refers to conditions where apnea, hypopnea, respiratory effort-related arousals (RERAs), or all other abnormal reductions in gas exchange are present during sleep (Tsara, Amfilochiou, Papagrigorakis, Georgopoulos, & Liolios, 2009). *Apnea* is defined as cessation of respiratory airflow or less than 10% of baseline airflow for at least 10 s. *Hypopnea* is defined as either a >30% decrease in airflow from baseline lasting at least 10 s associated with a 4% oxygen desaturation or a decrease in flow by >50% of baseline for at least 10 s associated with a 3% oxygen desaturation. *Respiratory effort-related arousal* is defined as an arousal from sleep following a sequence of breaths that lasts at least 10 s, characterized by increasing

Modulation of Sleep by Obesity, Diabetes, Age, and Diet. http://dx.doi.org/10.1016/B978-0-12-420168-2.00040-5

respiratory effort or flattening of the nasal pressure wave form, which does not meet the criteria for an apnea or hypopnea (Berry et al., 2012).

Respiratory disturbance index (RDI) is the total number of apneas, hypopneas, and RERAs per hour of sleep.

Obstructive sleep apnea is diagnosed when either of two conditions is confirmed (Epstein et al., 2009):

- RDI ≥ 15 in an asymptomatic patient.
- RDI ≥ 5 in a symptomatic patient.

Apnea-hypopnea index (AHI) is the total number of apneas and hypopneas per hour of sleep. The AHI is generally smaller than the RDI, because the AHI does not include the frequency of RERAs, while the RDI does (Tsara et al., 2009).

AHI is the primary metric used to report polysomnography results, and severity of OSA is traditionally classified as mild, moderate, or severe on the basis of symptoms and AHI. *Mild OSA* is defined as an AHI between 5 and 15 events/h, *moderate OSA* as between 15 and 30 events/h, and *severe OSA* as greater than 30 events/h (Epstein et al., 2009).

The common symptoms of OSA are daytime sleepiness, snoring, or interruptions of breathing reported by a bed partner. Other symptoms that are suggestive of OSA are fatigue, tiredness, low energy, irritability, lack of concentration, memory impairment, and morning headaches.

Patients with OSA are at increased risk for hypertension, diabetes, coronary artery disease, cardiac arrhythmia, and stroke. Patients with untreated severe OSA have a threefold increased risk of mortality compared to individuals without OSA (Young et al., 2008).

Polysomnography is considered the gold-standard diagnostic test for OSA. This study involves several measured physiologic recordings such as electroencephalogram, electrooculogram, electrocardiogram, chin and leg electromyograms, body position, finger pulse oximetry, measurements of airflow, and measurements of thoracic and abdominal respiratory effort. Since polysomnography is an expensive and time-consuming test, portable monitoring is often used for diagnosis of suspected OSA in patients with a high pretest probability of having moderate to severe OSA and no comorbid medical or sleep disorders.

OBESITY AND SLEEP APNEA

A study in 1993 estimated that the prevalence of OSA (having both AHI ≥ 5 and daytime sleepiness) in middle-aged adults was 4% among men and 2% among women (Young et al., 1993). Another study in 2012 estimated that the prevalence of mild OSA had increased to 14% among men and 5% among women, with 13% of men and 6% of women having moderate to severe OSA (AHI ≥ 15) (Peppard et al., 2013).

Several risk factors may predispose one to the development of OSA. Undoubtedly, one of the strongest risk factors is obesity, and the rising prevalence of obesity is thought to be a likely reason for this increase in OSA. Other contributing risk factors include age, male gender, menopause, craniofacial abnormalities, nasal congestion, upper airway anatomy, smoking, alcohol, and genetic predisposition (Young, Skatrud, & Peppard, 2004).

Several studies demonstrate that obesity is a strong risk factor for OSA and there is a direct relationship between the OSA epidemic and the obesity epidemic (Peppard, Young, Palta, Dempsey, & Skatrud, 2000; Restal et al., 2001; Tishler, Larkin, Schluchter, & Redline, 2003; Young et al., 2004). A study of 161 consecutive obese patients with a BMI greater than 40 kg/m^2 found OSA (RDI ≥ 10) to be present in more than 50% (Resta et al., 2001). For each unit increase in BMI, the odds ratio for developing OSA is 1.14 (95% confidence interval 1.10–1.19) (Tishler et al., 2003), and with a BMI increase of 5.67 kg/m^2, the odds ratio for developing OSA is 4.17 (Young et al., 1993). A 10% weight gain predicted an approximate 32% increase in the AHI and sixfold increase in the odds ratio for developing OSA (AHI ≥ 15) (Peppard et al., 2000).

Obesity has been found to cause OSA by numerous mechanisms, including change in upper airway geometry, increased collapsibility of airway, reduced chest wall compliance, reductions in functional residual capacity, and increased whole-body oxygen demand (Young, Peppard, & Taheri, 2005).

Obesity increases the risk for OSA, but OSA on the other hand may predispose the individual to weight gain (Tuomilehto, Seppä, & Uusitupa, 2013). Daytime sleepiness from OSA can decrease physical activity and energy expenditure. Also, sleep fragmentation of OSA is associated with decreased leptin levels and increased ghrelin levels, which results in the increase of both hunger and appetite (Newman et al., 2005). Obesity and OSA therefore seem to form a vicious spiral in which they negatively impact one another.

The impact of increase in BMI on OSA appears to be less significant after the age of 60 (Tishler et al., 2003). It has been shown that BMI has a smaller influence on AHI in the elderly population as compared to middle-aged individuals, and furthermore, changes in BMI, particularly weight gain, have a lesser impact on the severity of OSA in the elderly (Bixler et al., 2001; Bixler, Vgontzas, Ten Have, Tyson, & Kales, 1998; Young et al., 2005). Also, OSA is more closely related to BMI in men than in women. Women tend to develop OSA at much higher levels of obesity than men. There is also a tendency for an acceleration of worsening OSA with more extreme weight gain in patients who were already overweight or obese (Newman et al., 2005). Therefore, weight reduction potentially has a greater impact on OSA in middle-aged severely obese men than in women.

BARIATRIC SURGERY: THE PRESENT STATE

Bariatric surgery (Figure 1) is now considered the most effective treatment for morbid obesity, producing durable weight loss, improvement or remission of comorbid conditions, and longer life expectancy (SAGES, 2008). Bariatric surgery is reported to be associated with a mean excess weight loss (EWL) of 67.1% and 89% reduction in the relative risk of mortality (Christou et al., 2004). The overall mortality rate of bariatric surgery in high-volume bariatric surgery centers is as low as 0.13% (Ballantyne et al., 2008). The leading cause of mortality after bariatric surgery is pulmonary embolism (Al Harakeh, 2011).

The first operation for morbid obesity, the jejunoileal bypass, was first performed in 1954. However, it later became evident that this purely malabsorptive procedure had unacceptable morbidity and mortality related to bacterial overgrowth and liver damage. In 1967, the first gastric bypass procedure with a loop gastrojejunostomy was described by Mason, and in 1977 it was modified to a Roux-en-Y reconstruction by Griffen. In 1976, biliopancreatic diversion (BPD) was first described by Scopinaro et al., and it was eventually modified to duodenal switch (DS) in the1990s (SAGES, 2008). Laparoscopic adjustable gastric banding was first described in the early 1990s. Sleeve gastrectomy, originally performed as part of staged procedure (i.e., part 1 of BPD/DS), is now considered an effective bariatric procedure in and of itself and thus has gained significant popularity since the early 2000s.

One survey revealed that the total number of bariatric surgeries performed globally in 2011 was reported to be more than 340,000 cases, with the most commonly performed procedures being Roux-en-Y gastric bypass (RYGB) 46.6%; sleeve gastrectomy (SG) 27.8%; adjustable gastric banding (AGB) 17.8%; and BPD/DS 2.2% (Table 1). There has been a significant increase in the numbers of SG performed since the early 2000s. Currently 90% of weight loss surgery is being performed laparoscopically (Buchwald & Oien, 2013).

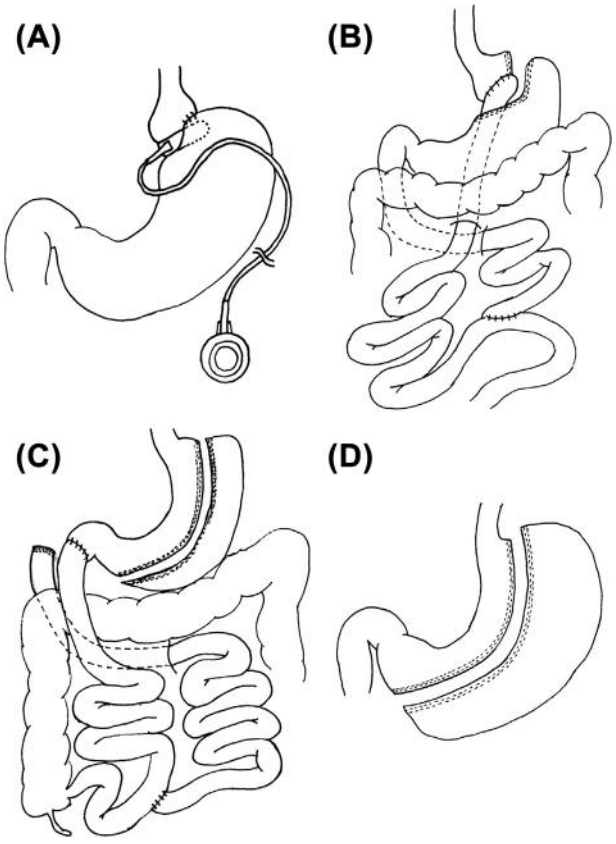

FIGURE 1 Bariatric procedures. (A) Adjustable gastric banding. (B) Roux-en-Y gastric bypass. (C) Biliopancreatic diversion + duodenal switch. (D) Sleeve gastrectomy.

Laparoscopic Adjustable Gastric Banding

Laparoscopic adjustable gastric banding (LAGB) is a purely restrictive procedure and has the lowest mortality rate (0–0.4%) among all bariatric surgeries (Ballantyne et al., 2008; SAGES, 2008). The stomach is encircled with a saline-filled silicone band just below the gastroesophageal junction to limit luminal diameter. The band is connected via tube to an injection port/valve placed subcutaneously along the abdominal wall. Injecting or withdrawing fluid through this port can help achieve appropriate restriction for the patient. The percentage of EWL (%EWL) at 1 year and 3 years after surgery is around 42.0% and 54.8%, respectively (O'Brien, MacDonald, Anderson, Brennan, & Brown, 2013).

Major complications of LAGB include band slippage and intragastric band erosion. Band slippage is the herniation of the distal stomach upward through the band. Patients may present with vomiting, severe acid reflux, or cessation of weight loss. With intragastric band erosion, the band erodes through the gastric wall into the gastric lumen

TABLE 1 Features of Each Bariatric Surgery

	Worldwide Prevalence (%) in 2011	%EWL by 1 year	%EWL by 3 years	Mortality (%)
AGB	17.8	42.0	54.8	0–0.4
RYGB	46.6	67.3	62.5	0.4
BPD/DS	2.2	71.8	76.3	2.6–7.6
SG	27.8	49–81 (By 6 months to 3 years)		0.19

EWL, excess weight loss; AGB, adjustable gastric banding; RYGB, Roux-en-Y gastric bypass; BPD/DS, biliopancreatic diversion/duodenal switch; SG, sleeve gastrectomy.

secondary to gastric wall ischemia resulting from over-restriction of the band, band site infection, or intraoperative gastric wall injuries. Patients usually present with epigastric pain, cellulitis at the port site, hematemesis, or cessation of weight loss. The incidence of band slippage and band erosion is reported to be between 7% and 24% and between 0.3% and 14%, respectively (SAGES, 2008; Sonavane et al., 2012). Both of these complications usually require revisional surgery with or without band replacement. Other complications of LAGB include tubing- and port-related problems such as infection and leakage (10–15%), esophageal dilatation (6.6–10%), and gastric perforation (1.0%) (Nguyen, 2008; O'Brien, MacDonald, Anderson, Brennan, & Brown, 2013; SAGES, 2008).

Although LAGB was one of the more popular bariatric surgeries performed regularly (especially in Europe, where it was the most common bariatric procedure until around 2010), it is now less commonly performed secondary to difficulty in performing band adjustment, less efficacy for weight loss compared to other procedures, and a high revisional surgery rate (up to 33% in 9 years) (Buchwald & Oien, 2013; SAGES, 2008). There has been a decrease in the number of complications and revisional procedures performed due to improvements in the band itself as well as improved surgical technique, such as the pars flaccida approach (O'Brien et al., 2013; SAGES, 2008).

Roux-en-Y Gastric Bypass

Worldwide, the RYGB is still one of the most commonly performed bariatric surgeries, and it includes both a restrictive and a malabsorptive component. A surgical stapler is used to create a small vertically oriented gastric pouch with a volume of roughly 15–30 cc. Jejunum is divided 15–40 cm from the ligament of Treitz and a jejuno-jejunal anastomosis is performed to create a 75–150-cm-long Roux limb, which is then anastomosed to the newly created gastric pouch. This results in ingested food bypassing the excluded stomach, the entire duodenum, and the proximal jejunum. The %EWL at 1 year and 3 years is 67.3% and 62.5%, respectively (O'Brien, McPhail, Chaston, & Dixon, 2006).

Mortality rates for RYGB performed in centers of excellence are under 0.4% (Flum et al., 2009). Major early complications after RYGB include dehydration, pulmonary or venous thromboembolism, hemorrhage, anastomotic leakage, and bowel perforation. Late complications include internal hernia formation, vitamin deficiencies, cholelithiasis, intestinal obstruction, and marginal ulcers (Neff & le Roux, 2013). Anastomotic leakage is the second-leading cause of mortality, following pulmonary embolism. Leakage can occur not only at the gastrojejunal and jejuno-jejunal anastomoses but also at any other staple line, and may cause peritonitis with sepsis. The incidence of anastomotic leakage ranges from 0% to 5.6% in large series. Internal hernia formation usually occurs later in the postoperative course and is the most common cause of intestinal obstruction following RYGB. Hernia formation may cause bowel strangulation and can sometimes lead to fatality. The incidence of internal hernia formation after laparoscopic RYGB is 3–4.5%, which is reported to be higher than that of open RYGB (Al Harakeh, 2011).

Biliopancreatic Diversion/Duodenal Switch

In the original BPD procedure described by Scopinaro in 1976, a horizontal partial gastrectomy was performed with formation of a 400 ml gastric pouch. The small intestine was then divided 250 cm proximal to the ileocecal valve and the alimentary limb was connected to the gastric pouch. An anastomosis was then performed between the distal end of the biliopancreatic limb and the side of the alimentary limb at a point 50–100 cm proximal to the ileocecal valve.

DS is a modification of BPD aimed to decrease complications including dumping syndrome and anastomotic marginal ulcer formation. In DS, a vertical sleeve gastrectomy is performed and the duodenum is then divided distal to the pylorus. The small bowel is then divided 250 cm proximal to the ileocecal valve. The alimentary limb is then connected to the proximal duodenal stump. The biliopancreatic limb is anastomosed to the ileum at a point 75–100 cm proximal to the ileocecal valve.

The %EWL after BPD/DS at 1 year and 3 years are 71.8% and 76.3%, respectively. A systematic review found that BPD resulted in more weight loss and improvement of comorbidities than any other bariatric surgery procedure (O'Brien et al., 2006). Despite these favorable reports, BPD/DS has been slow to gain widespread acceptance as it is a technically more difficult procedure to perform, has higher incidence of postoperative complications and vitamin deficiencies, and has an overall higher mortality rate (2.6–7.6%) (Kim et al., 2003; Paiva, Bernardes, & Suretti, 2002). BPD/DS may be reserved for super-morbidly obese patients whose aim is to achieve maximum weight loss.

Laparoscopic Sleeve Gastrectomy

Laparoscopic sleeve gastrectomy (LSG) involves resection of 70–80% of stomach along the greater curvature and creation of the long gastric tube ("sleeve") along the lesser curvature, while preserving the pylorus and distal antrum. LSG was initially described as part 1 of a 2-staged biliopancreatic diversion or duodenal switch. Recent reports have demonstrated that LSG is very effective as a primary bariatric procedure in and of itself. The mechanism of weight loss after LSG includes gastric volume restriction and, thus, patient-induced portion control, as well as alteration of gut hormones and gastric emptying. Technically, LSG is considered an easier operation to perform compared to the gastric bypass and is associated

with less vitamin deficiency, bowel obstruction, and marginal ulcer risk. Advantages of LSG compared to gastric banding include lack of foreign body, no need for adjustments, and no risk of slippage or erosion. Mortality rates are reported up to 0.19% (Berci, 2010). Recent systematic review demonstrated %EWL at 6 months–3 years ranging between 49% and 81%. Major postoperative complications include bleeding, leakage, and stricture formation (Trastulli et al., 2013).

IMPACT OF BARIATRIC SURGERY ON OBSTRUCTIVE SLEEP APNEA

An increasingly robust body of literature has shown that bariatric surgery can drastically improve OSA and sometimes achieve sustained OSA resolution (Sarkhosh et al., 2013). In 2004, Buchwald and colleagues published a meta-analysis based on 136 studies including 22,094 patients, where they found that OSA had resolved in 85.7% of patients after undergoing bariatric surgery (Buchwald et al., 2004). In 2013 Sarkhosh and colleagues published a systematic review of 69 studies including13,900 patients, where they reported the percentage of patients who experienced resolution or improvement of OSA after various bariatric procedures as follows: 79% after RYGB, 77% after LAGB, 86% after LSG, and 99% after BPD (Sarkhosh et al., 2013).

One perhaps limiting factor in the review of these articles was the variable definitions of OSA used, and that many studies had not performed polysomnography before and after bariatric surgery but had relied instead on subjective symptoms of patients. It is known that subjective symptoms correlate poorly with polysomnographic results (Weaver, Kapur, & Yueh, 2004) and cannot serve as a reliable indicator in patients with a high predicted probability of OSA, such as in obese patients (Viner, Szalai, & Hoffstein, 1991). Furthermore, obesity can be associated with excessive daytime sleepiness, a primary symptom of OSA, even in the absence of OSA (Resta et al., 2001). Therefore, based on those studies, the general perception that bariatric surgery cures OSA in more than 80% of patients may be inaccurate (Pannain & Mokhlesi, 2010).

For evaluating the impact of bariatric surgery on OSA based on objective polysomnography outcomes (Table 2), Greenburg and colleagues performed a meta-analysis of 12 studies on 342 patients who underwent clinical assessment and polysomnography before and at least 3 months after bariatric surgery (Greenburg, Lettieri, & Eliasson, 2009). They reported that bariatric surgery reduces BMI by 17.9 kg/m^2 (from 55.3 kg/m^2 to 37.7 kg/m^2) and was associated with a reduction of AHI by 38.2 events/h (from 54.7 events/h to 15.8 events/h). A total of 62% of patients following bariatric surgery had residual disease with a mean residual AHI of more than 15 events/h, which corresponds to moderately severe OSA. For the six studies in which individual patient data were reported, only 25% of patients achieved resolution of OSA attaining an AHI of fewer than 5 events/h. According to these results, which were based on polysomnographic data, the resolution rate of OSA appears to be lower than those of studies based purely on subjective symptoms.

Limitations of Greenburg's meta-analysis may be that some of the studies included had insufficient and varying

TABLE 2 Description of Studies of Efficacy of Bariatric Surgery on Obstructive Sleep Apnea Based on Polysomnography

First Author	Greenburg	Fritscher	Lettieri	Ravesloot
Study type	Meta-analysis	Cohort	Cohort	Cohort
Year	2009	2007	2008	2013
Sample size	342	13	24	171
Procedure	Various	RYGB	RYGB	AGB + RYGB + SG
Follow-up period	Various (>3 months)	1 year	1 year	17 months
Decrease in mean BMI (kg/m^2)	55.3→37.7	55.5→34.1	51.0→32.1	45.0→35.0
Decrease in mean AHI (events/h)	54.7→15.8	46.5→16.0	47.9→24.5	44.1→17.4
Cure rate	25%	25%	4%	25%
Improvement rate	n/a	75%	96%	82%
Limitations	Insufficient follow-up period in some studies. A number of patients missed follow-up polysomnography	Insufficient sample size	Insufficient sample size	A Number of patients missed follow-up polysomnography

OSA, obstructive sleep apnea; RYGB, Roux-en-Y gastric bypass; AGB, adjustable gastric banding; SG, sleeve gastrectomy; BMI, body mass index; AHI, apnea-hypopnea index.

follow-up periods that were too short for obtaining the maximum weight loss usually seen after bariatric surgery, many patients missed follow-up polysomnography, and an insufficient number of patients studied yields low study power. Among this meta-analysis were two prospective studies in which most of the included patients had reevaluation with polysomnography after a sufficient follow-up period. Fritscher and colleagues' prospective study included 13 patients who underwent polysomnography before laparoscopic RYGB (LRYGB) and 12 patients who underwent follow-up polysomnography at 18 months after surgery. The mean BMI decreased from 55.5 to 34.1 kg/m^2 and the mean AHI decreased from 46.5 to 16.0 events/h. Three patients (25%) experienced resolution of OSA (AHI < 5) and 9 patients (75%) experienced decrease in AHI (Fritscher et al., 2007). Lettieri and colleagues' prospective study included 24 patients who all underwent polysomnography before and 1 year after LAGB. They reported that the mean BMI decreased from 51.0 to 32.1 kg/m^2 and the mean AHI decreased from 47.9 to 24.5 events/h. Among those patients, only 1 patient (4%) experienced complete resolution of OSA (AHI < 5) and 23 patients (96%) experienced decrease in AHI (Lettieri, Eliasson, & Greenburg, 2008). Their results are perhaps more reliable as almost all of their patients had follow-up polysomnography after a sufficient follow-up period. However, potential limitations include small sample size and most of the patients they analyzed fell into the super-morbidly obese category.

A prospective study published in 2013, by Ravesloot and colleagues, contains a comparatively large number of patients with sufficient follow-up. They followed 171 patients who underwent polysomnography before bariatric surgery (LAGB, LRYGB, and LSG) and again 7 and 17 months after surgery. They reported a reduction in mean BMI from 45.0 to 36.7 to 35.0 kg/m^2, and a reduction in mean AHI from 49.1 to 22.7 to 17.4 events/h. The resolution rate of OSA (AHI < 5) at 17 months after the surgery was 24%, and 82% (41 patients) experienced an overall decrease in AHI. The limitation of their study was once again the low percentage of the patients that had follow-up polsysomnography analysis; 64.3% had follow-up polysomnography 7 months after the surgery and only 29.4% had follow-up polysomnography 17 months after the surgery. They attributed the reason for such a low follow-up percentage to the belief that most patients deemed a second evaluation unnecessary, as their symptoms had subsided. They therefore may have underestimated the success rate, as only patients with residual symptoms were keen for reevaluation (Ravesloot, 2013).

In order to assess the impact of bariatric surgery on OSA, it should be stated that resolution rates of OSA following bariatric surgery appear to be variable (4–25%) and improvement rates of OSA following bariatric surgery appear to be high (75–96%) (Fritscher et al., 2007; Greenburg et al., 2009; Lettieri et al., 2008; Ravesloot, Hilgevoord, van Wagensveld, & de Vries, 2013). This can perhaps be explained by the fact that while many patients obtain dramatic weight loss following bariatric surgery, most patients still fall into the obese category (BMI >30) and are thus still at risk for OSA. Also, while obesity is the strongest risk factor for OSA, there are many other risk factors that cause OSA, including craniofacial abnormalities, upper airway anatomy, nasal congestion, smoking, alcohol, and genetic predisposition. Although bariatric surgery may offer drastic improvement in OSA severity, patients may still have moderate OSA and may benefit from further treatment modalities such as continuous positive airway pressure (CPAP), oral appliances, and surgery.

Do patients benefit from a decrease in AHI without complete resolution? A prospective study following 14,589 patients for 4.6 years showed that an increasing severity of OSA is associated with increased all-cause mortality in men <50 years old; males with RDI > 30 had a significantly higher mortality hazard rate than the reference group of males with RDI < 10 and there was a significant linear increase in mortality hazards with RDI (Lavie, Lavie, & Herer, 2005). It is also reported that severe OSA (AHI > 30) is associated with increased cardiovascular mortality in women (Campos-Rodriguez et al., 2012), and increasing severity of OSA is associated with poor glucose control in patients with type 2 diabetes (Aronsohn, Whitmore, Van Cauter, & Tasali, 2010). Furthermore, CPAP pressure requirements decrease considerably with decrease in AHI, which potentially improves tolerance of and compliance with CPAP (Lankford, Proctor, & Richard, 2005). Therefore, decreased AHI after bariatric surgery may be potentially beneficial to patients with OSA even if they do not obtain complete resolution of OSA.

THE KEY TO TREATING OBSTRUCTIVE SLEEP APNEA WITH BARIATRIC SURGERY

For diagnosis of OSA, polysomnography analysis is an indispensable tool, especially among bariatric patients. The prevalence of OSA in patients considered for bariatric surgery is very high and has been reported to be as high as 93.6% in men and 73.5% in women (Sareli et al., 2011). However, OSA is significantly underdiagnosed in these patients (Rasmussen, Fuller, & Ali, 2012). Because of the high prevalence rate of OSA in bariatric patients, subjective symptoms alone should not serve as a reliable screening test (Viner et al., 1991). If OSA is unidentified and left untreated, patients will have a higher probability of cardiac or pulmonary complications, both perioperatively and postoperatively (Elshaug, Moss, Southcott, & Hiller, 2007). Therefore, ideally, all patients considered for bariatric surgery should undergo polysomnography before surgery.

Although bariatric surgery offers significant improvement in OSA, patients should be treated comprehensively with

other treatment modalities as well. One study estimated that 17% of middle-aged adults in the general population have AHI≥5, and in 41% of them OSA is attributable to excess weight. Similarly, it is estimated that 5.7% of adults have AHI≥15, and in 58% of them OSA is attributable to excess weight (Young et al., 2005). These data suggest that in about half of those suffering from OSA, their disease may not be caused by excess weight alone. Also, it is reported that 26% of normal-weight 50- to 69-year-old men suffer from OSA (Young et al., 2005). Therefore, obesity may not be the only causative agent contributing to OSA, and some patients may benefit from other treatments modalities such as CPAP, oral surgeries, and oral appliances. These treatment modalities, on the other hand, also cannot achieve a complete resolution of OSA in most cases. It is reported that only 13% of the patients who undergo oral surgery can obtain AHI≤5 (Elshaug et al., 2007). Also 46–83% of patients with OSA have been reported to be nonadherent to CPAP therapy (Weaver & Grunstein, 2008). With resolution rates of OSA after bariatric surgery being reported at 4–25% and the improvement rates of OSA following bariatric surgery at 75–96%, bariatric surgery may be the most effective treatment for OSA. However, it should be noted that there is a limitation in the efficacy of bariatric surgery alone on OSA, and patients may benefit from the other treatment modalities as well.

Following bariatric surgery, patients should be followed for OSA on a long-term basis. There are patients who undergo bariatric surgery who may experience some weight regain in the long term, which may worsen OSA. Furthermore, a study showed that some patients post bariatric surgery experience worsening of OSA despite no significant weight regain (Pillar, Peled, & Lavie, 1994). This finding may be due to aging, in and of itself a known risk factor for developing OSA. Consequently, even if patients obtain a resolution or improvement of OSA following bariatric surgery, they should still be followed up and monitored for possible recurrence or deterioration of OSA.

In conclusion, when bariatric surgery is considered as a treatment option for OSA, patients should be well informed that although bariatric surgery is very effective at ameliorating OSA, surgery alone may not always achieve complete resolution of OSA, they will require long-term follow-up after surgery, and they should continue CPAP treatment or additional treatment modalities that may be required for management of OSA.

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Chapter 41

Preoperative, Perioperative, and Postoperative Considerations in the Bariatric Surgery Patient with Sleep Apnea

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OBESITY AND OBSTRUCTIVE SLEEP APNEA

Obesity, defined by a body mass index (BMI) greater than 30 kg/m^2, is a common cause of preventable death in the United States (Salem, Jensen, & Flum, 2005). In fact, more than 400,000 annual deaths are attributed to obesity and its complications (Mokdad, Marks, Stroup, & Gerberding, 2004), and this growing epidemic is not simply an American problem. The prevalence of overweight and obesity has increased worldwide over the past several decades and in the United States now represents approximately 68% of the adult population (Flegal, Carroll, Ogden, & Curtin, 2010). Obesity is seldom present in isolation, and the problem of overweight and obesity is commonly associated with multiple comorbid conditions. The culmination of these factors is that obesity in general, and visceral adiposity specifically, is associated with an increased mortality. The overall relative risk of mortality is approximately 2.00 for men and 1.65 for women with a BMI greater than 35 kg/m^2, compared with the normal weight population. Moreover, the impact of obesity and its comorbidities can have long-lasting effects, with obesity in an otherwise healthy population in the fifth decade of life being associated with frailty decades later (Pischon et al., 2008; Standberg et al., 2012). The commonly described obesity-related comorbid conditions include type 2 diabetes, hypertension, degenerative joint disease, and obstructive sleep apnea (OSA), which account for significant morbidity and mortality in this population, and significant utilization of health care resources as well (Ghiassi, Morton, Bellatorre, & Eisenberg, 2012). The overall annual medical costs attributed to an individual who is obese are 42% greater than a person of normal weight. In fact, the costs attributed to obesity and its related conditions were estimated to be $147 billion for 2008 (Finkelstein, Trogdon, Cohen, & Dietz, 2009).

Sleep-disordered breathing is very common among the obese population, and obesity is believed to predispose to the development of OSA. Increased soft tissue mass in the mouth and oropharynx is thought to lead to relative airway obstruction during sleep, when supporting muscles relax. When severe, this leads to obstructive apnea (Schwab et al., 2003). This mechanism alone is not sufficient, however, and studies suggest that skeletal structure, neuromuscular and metabolic function, in addition to age and gender, also contribute to onset of OSA (Ravesloot, Hilgevoord, van Wagensveld, & de Vries, 2014). Nonetheless, in this context it is not surprising that the prevalence of OSA has increased in parallel with the increase in overweight, obesity, and morbid obesity. In fact, the incidence of OSA has been shown to increase in direct proportion to the level of obesity, such that the incidence of OSA in the morbidly obese population (the population with a BMI greater than 40 kg/m^2) is 12–30 times greater than in the normal weight population, and its prevalence may be as high as 80% in some reports (ASMBS, 2012; Bell & Rosenbaum, 2005; Kyzer & Charuzi, 1998; O'Keeffe & Patterson, 2004; Rasheid et al., 2003). Complicating these numbers is the fact that most adults with OSA

Modulation of Sleep by Obesity, Diabetes, Age, and Diet. http://dx.doi.org/10.1016/B978-0-12-420168-2.00041-7

are likely undiagnosed (Young, Evans, Finn, & Palta, 1997). This is especially important in the morbidly obese population, because this population is already at risk for multiple medical problems. This is compounded by the presence of OSA, which alone has been associated with an increased risk of type 2 diabetes, hypertension, cardiac arrhythmias, first stroke, nocturnal sudden death, and all-cause mortality (Gami, Howard, Olson, & Somers, 2005; Marshall et al., 2008; Mehra et al., 2006; Parra et al., 2000; Somers, Dyken, Clary, & Abboud, 1995; Tasali, Mokhlesi, & Van Cauter, 2008) as well. Thus, these findings together suggest that the morbidly obese individual with OSA is especially high risk and requires special attention in consideration for elective surgery.

PREOPERATIVE ASSESSMENT

The presence of OSA in a severely or morbidly obese individual undergoing bariatric (or any abdominal) surgery requires a meticulous preoperative evaluation. Since OSA is often present in the morbidly obese population and has a significant impact on both the perioperative and postoperative course of the bariatric patient, it is important to establish the diagnosis of OSA early in the preoperative assessment.

Although associated with obesity, it is clear that BMI alone is an insufficient tool to screen for OSA. Multiple questionnaires and assessment tools have been developed to screen surgical and bariatric patients for the presence of OSA. These tools include the STOP questionnaire, Berlin questionnaire, and Epworth Sleepiness Scale, and they have been shown to have a moderately high sensitivity, but low specificity, to screen surgical patients for OSA when used in combination with other factors such as BMI, gender, and American Society of Anesthesia checklist (Chung et al., 2008a; Chung et al., 2008b; Neto, Brandao, Loli, Leite, & Weber, 2013). These tools rely on patient self-assessment, and potential bias is anticipated, especially in the patient population being evaluated for bariatric surgery. These patients may be incentivized to minimize their symptoms in the hope that their chances to be approved for surgery will be increased. Yet, these tools in combination with other clinical data can suggest undiagnosed OSA with high degree of reliability. Nonetheless, some argue that all patients being evaluated for bariatric surgery should be objectively evaluated with polysomnography (PSG), since clinical screening alone underestimates the prevalence of the disease and many patients proceeding to bariatric surgery remain underdiagnosed (Lopez, Stefan, Schulman, & Byers, 2008; O'Keeffe & Patterson, 2004; Ravesloot et al., 2014).

Routine PSG for all morbidly obese patients being evaluated for bariatric surgery, however, is consuming of time and resources, and in many institutions impractical. Moreover, some have argued that clinical evaluations alone, without PSG, have not resulted in increased postoperative pulmonary complications (Jensen et al., 2008), thus arguing that a clinical evaluation alone is sufficient.

In our practice, at the Palo Alto VA Bariatric Surgery Program, we selectively refer patients for preoperative objective testing for OSA based on clinical history and symptoms. All morbidly obese patients (or patients with severe obesity and related comorbid conditions) are evaluated by a multidisciplinary team, which includes a surgeon, bariatrician, dietitian, exercise physiologist, and psychologist, based on National Institutes of Health consensus guidelines (Gastrointestinal Surgery, 1996). Those patients with a known history of OSA are followed to ensure compliance with medical treatment. Those who do not have a history of OSA are screened with a brief questionnaire and anthropometric measures. The patients who are deemed high risk, based on the questionnaire, are then referred to undergo PSG for diagnosis and followed with treatment (Figure 1). With very few exceptions, all patients with properly treated OSA will then be referred for bariatric surgery.

The first-line approach to medical treatment of sleep apnea is the use of continuous positive airway pressure (CPAP). CPAP has been shown to have beneficial effects on objective measures of OSA within several weeks of use, including improved apnea-hypopnea index (AHI) and normalization of oxygen saturation (Gay, Weaver, Loube, & Iber, 2006). In our practice, we insist on its use by all of our patients who carry the diagnosis of moderate to severe sleep apnea. For patients who are newly diagnosed with OSA, we offer bariatric surgery only after at least 1 month of the initiation of CPAP therapy, although there is no evidence to support waiting any specific amount of time before surgery.

This approach to preparing morbidly obese patients with sleep apnea for bariatric surgery depends heavily on patient cooperation in their own treatment plan. Unfortunately, we have found that compliance with CPAP treatment, as prescribed, is not greater than 50% in our patient population. Poor adherence to CPAP therapy, however, appears to be a common problem in both surgical and nonsurgical patients (Sawyer et al., 2011; Wolkove, Baltzan, Kamel, Dabrusin, & Palayew, 2008).

PERIOPERATIVE CONSIDERATIONS

As discussed, the increase in soft tissue mass of pharyngeal tissues is thought to contribute, at least in part, to OSA in the obese population. This is compounded by the use of analgesics or anesthetic agents, which can decrease pharyngeal muscle tone, and thus exacerbate obstruction. For this reason, intraoperative airway management can prove to be challenging. Many anesthetic agents that are in common use have been shown to promote relative pharyngeal collapse in obese patients (Benumof, 2002). In addition, the central response to relative obstruction may be further blunted by opioids or anesthetics. The use of regional anesthesia is

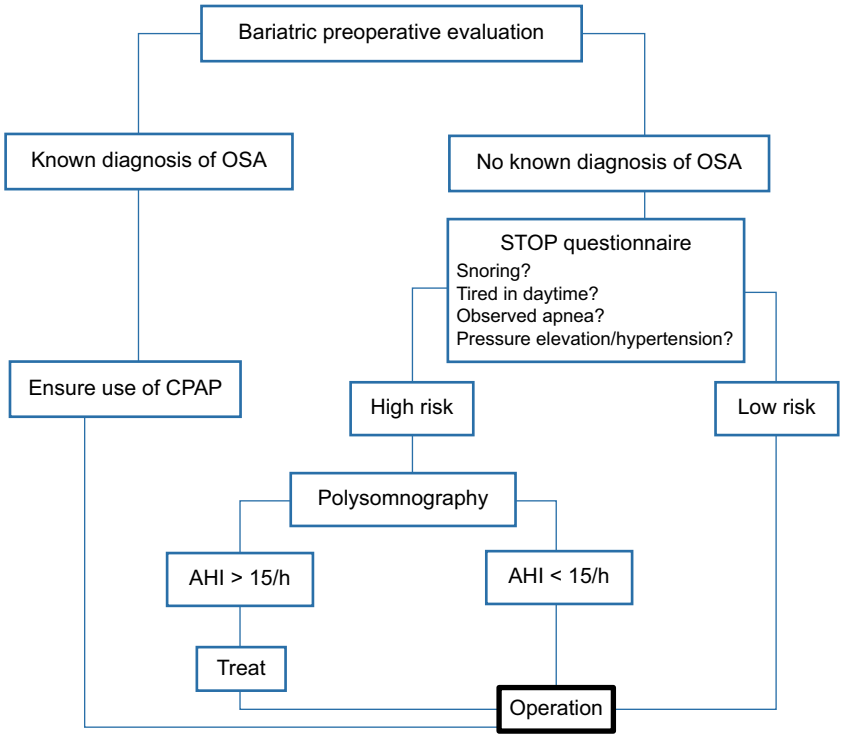

FIGURE 1 Assessment for obstructive sleep apnea in the obese patient being evaluated for bariatric surgery at the Palo Alto VA hospital. OSA, obstructive sleep apnea; CPAP, continuous positive airway pressure; AHI, apnea-hypopnea index.

often favored, in helping reduce the dose of sedation and opioids used. However, bariatric surgery can only be performed under general anesthesia. Moreover, most bariatric operations are now performed using a minimally invasive, or laparoscopic, approach, for which supplementing regional anesthesia has not been shown to add benefit.

It is unclear whether severe obesity, in and of itself, is associated with a more difficult intubation than in normal weight individuals (Brodsky, Lemmens, Brock-Utne, Vierra, & Saidman, 2002). However, it appears that the combination of a short neck and large neck circumference provides the more important determining factors, more so than BMI itself. Interestingly, these are the same anatomical features that are associated with OSA. Thus, OSA is found to be associated with a nearly 10-fold increase risk of a difficult intubation (Siyam & Benhamou, 2002). For this reason, a considerable amount of attention is focused on patient preparation for intubation. Maneuvers to elevate and support the patient's upper body and head improve the anesthesiologist's view of the larynx and enhance the safety and success of intubation (Collins, Lemmens, Brodsky, Brock-Utne, & Levitan, 2004).

In the postanesthesia care unit (PACU), the bariatric patient with OSA requires close attention. Decreased respiratory drive and relaxation of pharyngeal muscles due to residual anesthetic medications, or introduction of postoperative intravenous analgesia, may lead to significant and rapid respiratory compromise. Considering that these patients already may be difficult to intubate electively, an airway emergency may result in a clinical disaster. Therefore, these patients need to be monitored closely and analgesic agents need to be administered judiciously. In our hospital, patients who underwent bariatric surgery are watched for a slightly longer period of time than other patients, and somnolence or changes in vital signs are treated aggressively. In addition, the patients are frequently assessed by the nursing and anesthesiology staff during the early recovery period from general anesthesia.

POSTOPERATIVE CONSIDERATIONS

After surgery and discharge from the PACU, the patient may be transferred to the intensive care unit (ICU), intermediate care unit, or standard ward. There are little high-level data to argue for the disposition of the patient to one versus another unit. There is some evidence, however, to suggest that routine elective admission to the ICU after bariatric surgery for patients with OSA is unnecessary (Grover et al., 2010; Shearer, Magee, Lacasia, Raw, & Kerrigan, 2013). This is an important finding, as the ICU is a resource with limited availability and of high cost in most hospitals. Thus, patients can be safely managed in an intermediate-level ward. This is contingent upon close (continuous) monitoring of oxygen saturation and/or hypercapnea with judicious administration of analgesics.

Opioid analgesics are especially dangerous in the postoperative OSA patient. Intense rapid eye movement sleep leads to paralysis of the genioglossus muscle and

retroglossal space obstruction, which is further enhanced by narcotics and sedatives. In addition, OSA patients are at risk for respiratory depression from opioid administration in any form (i.e., oral, epidural, intravenous), which in severe cases can lead to sudden death (Bell & Rosenbaum, 2005; Ostermeier, Roizen, Hautkappe, Klock, & Klafta, 1997).

In our practice, we treat pain with a patient-controlled anesthesia delivery of intravenous hydromorphone. However, patients are also given routine intravenous acetaminophen to minimize the need for opioid use. Concurrently, the patients are positioned with the head of bed elevated to 30° at all times, encouraged out of bed in the early postoperative period, and monitored with continuous pulse oximetry. First-line therapy in the setting of respiratory depression is supplemental oxygen, body positioning, CPAP, and intravenous naloxone to reverse the effects of narcotics.

CPAP and, to a lesser degree, bilevel positive airway pressure (BiPAP) is the mainstay of treatment for OSA. Early in the experience of bariatric surgery, patients with OSA were discouraged from using CPAP or BiPAP after surgery, for fear that increased oropharyngeal, esophageal, and proximal gastric pressure will lead to anastomotic leaks or staple line disruptions (Vasquez & Hoddinott, 2004) (Figure 2). Directed studies, however, testing the pressure effects of CPAP on the newly created stomach after bariatric surgery failed to demonstrate a significant increase in transmural pressure and consequently supported the use of CPAP in these patients (Weingarten et al., 2011).

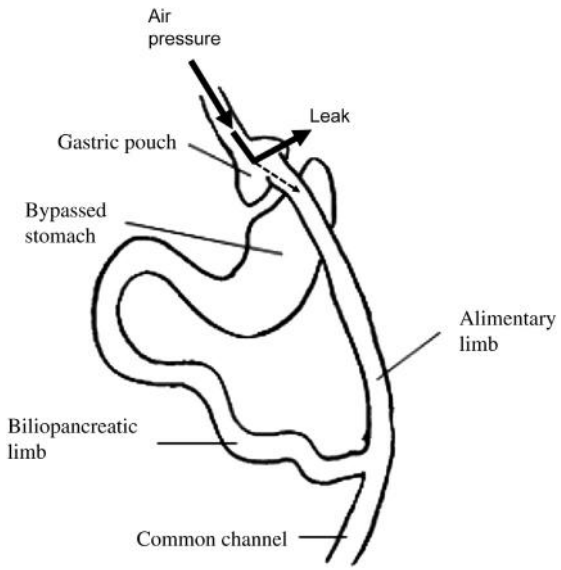

FIGURE 2 Schematic of Roux-en-Y gastric bypass demonstrating potential concern for leak due to introduction of positive airway pressure into the esophagus and gastric pouch. Solid arrow demonstrates potential build up of pressure that leads to a leak at the gastrojejunal anastomosis. Small arrow shows passage through intact anastomosis.

In fact, the postoperative use of CPAP has been shown to decrease pulmonary complications after bariatric surgery (Huerta et al., 2002). We recommend our patients with OSA initiate CPAP treatment early in the postoperative period. In fact, we counsel our patients to bring their own CPAP machines from home on the day of surgery, to ensure the appropriate settings and best fit of the facemask or nasal attachment.

EFFECT OF BARIATRIC SURGERY ON OSA

Bariatric surgery has emerged as the most effective and durable method for weight loss in the morbidly obese, as defined by a BMI greater than 40 kg/m^2 or, in the severely obese with BMI greater than 35 kg/m^2 who have associated comorbid conditions (Gastrointestinal Surgery, 1996; Sjostrom et al., 2007). Studies have consistently demonstrated the efficacy of several bariatric operations in producing significant weight loss for more than 5 and 10 years after surgery (Buchwald et al., 2004; Chang et al., 2014). Along with weight loss, postoperative bariatric surgery patients were also shown to have significant improvement or remission of associated comorbid conditions, including diabetes, hypertension, and OSA (Brethauer et al., 2013; Buchwald & Oien, 2013;Haines et al., 2007).

With respect to OSA specifically, Haines et al. demonstrated that surgical weight loss in patients with OSA resulted in a significant increase in oxygen saturation, decrease in respiratory distress index, and decrease in the settings or cessation of the use of CPAP (or BiPAP). Meanwhile, a meta-analysis of 342 patients demonstrated a significant reduction in the AHI after bariatric surgery (Greenburg, Lettieri, & Eliasson, 2009). The authors cautioned, however, that a portion of the postoperative population could have persistent, although improved, OSA that requires continued treatment and follow-up. The effect of bariatric surgery on objective OSA parameters occurs as soon as 1 month after surgery, is most dramatic within the first 7 months, and persists at least up to 17 months postoperatively (Ravesloot et al., 2014; Varela, Hinojosa, & Nguyen, 2007). In studies of thousands of patients, complete resolution or improvement in OSA objective parameters has been reported to range from 32% to 97% of patients after bariatric surgery (Buchwald et al., 2004; Haines et al., 2007; Wittgrove & Clark, 2000). Although all studies suggest excellent response to bariatric surgery, the wide range of results likely reflects the lack of standardization of postoperative reporting. As of yet, there is no standard method of assessing OSA and OSA improvement/resolution after bariatric surgery. Nonetheless, it is clear that after bariatric surgery, patients have a significant improvement in sleep apnea symptoms, and can often discontinue OSA treatment altogether.

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