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Sleep and Obesity: A focus on animal models

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Abstract

The rapid rise in obesity prevalence in the modern world parallels a significant reduction in restorative sleep (Agras et al., 2004; Dixon et al., 2007; Dixon et al., 2001; Gangwisch and Heymsfield, 2004; Gupta et al., 2002; Sekine et al., 2002; Vioque et al., 2000; Wolk et al., 2003). Reduced sleep time and quality increases the risk for obesity, but the underlying mechanisms remain unclear (Gangwisch et al., 2005; Hicks et al., 1986; Imaki et al., 2002; Jennings et al., 2007; Moreno et al., 2006). A majority of the theories linking human sleep disturbances and obesity rely on self-reported sleep. However, studies with objective measurements of sleep/wake parameters suggest a U-shaped relationship between sleep and obesity. Studies in animal models are needed to improve our understanding of the association between sleep disturbances and obesity. Genetic and experimenter-induced models mimicking characteristics of human obesity are now available and these animal models will be useful in understanding whether sleep disturbances determine propensity for obesity, or result from obesity. These models exhibit weight gain profiles consistently different from control animals. Thus a careful evaluation of animal models will provide insight into the relationship between sleep disturbances and obesity in humans.

In this review we first briefly consider the fundamentals of sleep and key sleep disturbances, such as sleep fragmentation and excessive daytime sleepiness (EDS), observed in obese individuals. Then we consider sleep deprivation studies and the role of circadian alterations in obesity. We describe sleep/wake changes in various rodent models of obesity and obesity resistance. Finally, we discuss possible mechanisms linking sleep disturbances with obesity.

Keywords

Sleep; obesity; sleep fragmentation; REM sleep; EDS; SWS-delta power; circadian clock; animal models

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I. Introduction

1.1. Fundamentals of Sleep

Sleep is a state of altered consciousness occurring as a natural and periodic phenomenon. During this state of rest, consciousness declines, motor output decreases and responsiveness to the environment is minimal (Greene and Siegel, 2004). Sleep can be distinguished from coma or anesthesia by its rapid reversibility into wakefulness. Sleep is important for many functions and a rebound increase in sleep follows sleep deprivation suggesting homeostatic control (Greene and Siegel, 2004). Sleep can be classified broadly into rapid eye movement (REM) sleep and non-rapid eye movement (NREM or non-REM) sleep with distinct electrographic wave forms in electro-encephalogram (EEG) and electromyogram (EMG) signals (Greene and Siegel, 2004). In humans, NREM sleep has been further divided into N1, N2, N3 and N4 stages based on specific EEG patterns. The N3 and N4 stages have been characterized by the presence of slow (delta) waves in the EEG and thus, referred also as slow-wave sleep (SWS). In the modern classification, the N3 and N4 stages have been combined as stage N3 and referred to as SWS (Silber et al. 2007). However, in animal literature, the terms SWS and NREM sleep have been used interchangeably and often refer to the same stage of sleep (non-REM sleep). Each stage of sleep has been proposed to have different functions, for example, NREM sleep has been thought to assist in nervous system restoration after prolonged wakefulness, protein synthesis, defense against oxidative stress and energy conservation (Borbély and Achermann, 1965; Greene and Siegel, 2004). REM sleep has been suggested to be important for memory consolidation, growth, neurogenesis and maturation of the nervous system (Siegel, 2005). Distinct neuronal populations in different brain areas generate NREM sleep and REM sleep. Forebrain areas generate NREM sleep mainly and brain stem structure trigger REM sleep (Greene and Siegel, 2004). Many neurotransmitter systems and neuropeptides, including but not limited to serotonin, norepinephrine, histamine, orexin, acetylcholine, prostaglandins and adenosine have been implicated in the regulation of this complex behavior. As mentioned before, many theories suggested a role for NREM sleep in energy conservation as energy expenditure was lowest during NREM sleep (Borbély and Achermann, 1965). Currently it is strongly believed that sleep plays an important role in energy homeostasis, and also that sleep disturbances increase risk for obesity, which affects one third of the population in the United States (Flegal et al., 2010).

1.2. Sleep disturbances among obese individuals

The study of the relationship between sleep and obesity dates back to the 1960s when investigators pointed out a link between body weight change and sleep disorders like narcolepsy and Pickwickian syndrome (Roberts, 1963; Ward and Kelsey, 1962). Recent epidemiological and animal studies supported these earlier observations and showed a crucial interplay between sleep and body weight regulation (Danguir, 1989; Guan et al., 2008; Jenkins et al., 2006; Kalra et al., 2008; Laposky et al., 2006; Liu et al., 2008; Megirian et al., 1998; Rao et al., 2009; Vgontzas et al., 2008). While it was recognized that 7–8 hours of uninterrupted sleep was optimal for adults, the reliance on self-reported sleep rather than objective measures (Marshall et al., 2008) has led to discrepancies in the literature focused on the relationship between sleep time and obesity, which has been extensively reviewed (Cappuccio et al., 2008; Marshall et al., 2008; Nielsen et al., 2011; Patel et al., 2008). Cross-sectional and cohort studies in children (Gupta et al., 2002; Nixon et al., 2008; Sekine et al., 2002; von Kries et al., 2002) clearly indicated an association between short sleep and weight gain. Longitudinal studies in adults (Gangwisch et al., 2005; Hasler et al., 2004; Lauderdale et al., 2006; Spiegel et al., 2004; Taheri et al., 2004; Vgontzas et al., 1998; Vorona et al., 2005) suggested greater weight gain or obesity with shorter nighttime sleep. In contrast, other studies showed an association between long-sleep duration, both at night and during

the day, and greater body weight (Vgontzas et al., 2008). When sleep/wake cycle was objectively measured, severe obesity was also associated with longer nighttime sleep in humans (Vorona et al., 2005; reviewed in Vgontzas et al., 2008). Overall studies are consistent with a bimodal or U-shaped relationship between sleep time and body weight gain in adults.

The presence of REM sleep during the active time period may impair energy metabolism and promote obesity in humans. Persons with narcolepsy/cataplexy, due to the loss of orexin-containing neurons or orexin receptors, had greater REM sleep propensity and more sleep onset REM periods during the active period (Cipolli et al., 2008; Nakamura et al., 2011, Kantor et al., 2009) and greater body mass index (BMI) than non-narcoleptics (Schuld et al., 2000). In addition, studies demonstrated that elevated body weight was associated with decreased nocturnal total sleep and REM sleep in humans (Dixon et al., 2005, Liu et al., 2008) and suggested that endocrine changes such as reduced leptin and increased ghrelin mediated the association between sleep and obesity (Liu et al., 2008). These endocrine changes are suggested to be more sensitive to reduced REM sleep at night (Liu et al., 2008). In contrast, weight loss in humans significantly increased the percentage of nighttime REM and SWS sleep (Dixon et al., 2005; Kalra et al., 2008). Together these studies indicate that normal amounts of REM sleep at night may be crucial for normal body weight maintenance and that the occurrence of more REM sleep during the day may increase the risk for higher BMI in humans. Though the effect of the absolute amount of sleep on body weight change seems bimodal, other factors including sleep fragmentation and excessive daytime sleepiness (components of sleep quality) appear to significantly impact body weight gain (Gangwisch and Heymsfield, 2004; Jennings et al., 2007; Moreno et al., 2006).

1.3. Sleep fragmentation

People with fragmented sleep had frequent sleep–wake transitions indicative of behavioral instability and thus were unable to remain asleep at night (Buysse et al., 1989; Unruh et al., 2006). These individuals fell asleep during the day and therefore sleep fragmentation at night contributed to excessive daytime sleepiness (EDS). Interestingly, total sleep duration (quantity) may not be different between persons with fragmented sleep and non-fragmented sleep. In contrast to persons with non-fragmented sleep, persons with excessive sleep fragmentation may self-report short total sleep duration.

Narcolepsy is a profound example of fragmented sleep characterized by multiple disjointed and abbreviated sleep and wake episodes rather than continuous and long episodes of sleep and wakefulness. However, sleep fragmentation has also been observed in non-narcoleptics (van den Berg et al., 2008a) and appeared to influence body weight gain, since excessive sleep fragmentation was a potent risk factor for the development of obesity (Stamatakis and Punjabi, 2010; van den Berg et al., 2008a; van den Berg et al., 2008b; von Kries et al., 2002). One accelerometer study, which objectively measured the presence or absence of body movement during the sleep/wake cycle, showed an association between sleep fragmentation and increased body weight in humans (van den Berg et al., 2008a). Moreover, bariatric surgery-induced weight loss reduced sleep fragmentation (Kalra et al., 2005). A recent study showed that sleep fragmentation without deprivation induced by auditory-tactile stimulation decreased insulin sensitivity in healthy volunteers (Stamatakis and Punjabi, 2010). Like humans, sleep fragmentation during the rest cycle led to sleepiness during the active period and absence of long wake bouts in rodents (McKenna et al., 2007; Stepanski et al., 1987). Likewise, narcoleptic mice with more fragmented sleep than wild-types lacked long wake bouts, had lower physical activity and gained more body weight (Zhang et al., 2007).

Collectively, these studies show a relationship between sleep fragmentation and obesity. The possible mechanism for this relationship might be excessive sleep fragmentation at night leading to daytime sleepiness, low physical activity, neurohumoral changes, altered insulin sensitivity, inflammation and altered glucose metabolism, which might perpetuate adiposity gain (Lanfranco et al., 2010; Mugnai, 2010; Stamatakis and Punjabi, 2010).

1.4. Excessive daytime sleepiness

Persons with EDS have reported sleepiness and fatigue during the day and population studies have documented a positive relationship between self-reported EDS and BMI (Resnick et al., 2006; Theorell-Haglow et al., 2006). Interestingly weight gain has been associated with disturbances in nocturnal sleep, EDS, and physical inactivity during the day (Vgontzas et al., 2008). Likewise, objective measurement of the sleep/wake cycle indicated that the presence of EDS symptoms was associated with greater body weight, in the presence or even in the absence of obstructive sleep apnea (OSA; Bixler et al., 2005; Resta et al., 2001; Resta et al., 2003; Vgontzas et al., 2008; Young et al., 1993). Excessive daytime sleepiness was also highly prevalent among patients with Prader-Willi syndrome, who exhibited hyperphagia and obesity (Vgontzas et al., 1995). These studies document that EDS seen in obese subjects can occur with or without sleep apnea and other nighttime sleep disturbances (Vgontzas et al., 2008). Similarly, studies have demonstrated that among obese subjects who self-reported sleep, those who slept more at night also exhibited EDS compared to subjects that slept less at night (Punjabi et al., 1999; Vgontzas et al., 1998). A recent review by Vgontzas and colleagues proposed a phenotypic dichotomy for EDS observed in obese persons to account for these paradoxical results and for the relationship between self-reported long and short time sleep with obesity (Vgontzas et al., 2008). In short, the first phenotype is characterized by “poor sleep, emotional distress, fatigue, and hypothalamic-pituitary-adrenal (HPA) axis ‘hyperactivity’”. This contrasts with the second phenotype, which is characterized by better sleep and no emotional distress, but had excess daytime sleepiness and either “normal or hypoactive” HPA axis activity (Vgontzas et al., 2008). Thus, it was hypothesized that self-perceived short sleep duration (despite normal or increased sleep when measured objectively) was a marker of emotional stress rather than a reflection of true sleep loss in obese individuals (Vgontzas et al., 2008). This again suggests that obesity may be associated with increased sleep duration since all of the above findings show a co-existence of EDS, sleep disturbances (fragmentation) and obesity.

2. Sleep deprivation studies

The above literature indicates that abnormal total sleep duration, excessive REM sleep during the active period, sleep fragmentation and EDS may singly or in combination alter physical activity and/or metabolism to induce weight gain. The relationship between sleep, body weight, physical inactivity and metabolism has been further supported by sleep deprivation studies, which have been reviewed (Everson and Toth, 2000; Novati et al., 2008; Ramanathan et al., 2002; Ramanathan et al., 2010; Rechtschaffen et al., 2002; Reynolds and Banks, 2010; Xu et al., 2010). A series of early animal studies showed that sleep deprivation by the disc-over-water (DOW) method resulted in weight loss (Rechtschaffen and Bergmann, 1995), unlike weight outcomes in human sleep deprivation studies. In this method, when the rat enters into sleep the disk rotates and the rat is carried towards water. To avoid falling into water, the rat must walk in the direction opposite to that of the disk rotation. Long-term sleep deprivation by this method resulted in initial hyperthermia, increased food intake, energy expenditure, body weight loss, skin lesions, oxidative stress, hypothermia at end stages and ultimately death (Ramanathan et al., 2002; Ramanathan et al., 2010; Rechtschaffen et al., 2002). However, several factors inherent to the DOW methods yet external to sleep deprivation likely contribute to the weight loss and eventual death observed among rodents sleep deprived by the DOW method. First, sleep deprivation by

DOW activates the HPA axis and increases corticosterone levels (Laposky et al., 2008b; Novati et al., 2008). The high frequency at which animals wake up when they fell into water highlights the plausibility that weight loss in the above studies may be due to physiological stress (Laposky et al., 2008b; Novati et al., 2008). Second, DOW-induced sleep deprivation may elevate metabolic rate due to increased thermoregulation and sympathetic activation resulting from the cold water immersion. This could contribute to the observed weight loss in this animal model. Cold stress and eventual hypothermia has long been suspected as a proximal cause of death in prolonged DOW, as rats show eventual declines in intra-peritoneal temperature, a reliable predictor of death (Rechtschaffen and Bergmann, 1995). Third, unlike human sleep restriction, rats sleep deprived by the DOW method have ulcerative and hyperkeratotic skin lesions, which is suggestive of catabolic breakdown of body tissues, potentially emanating from elevated metabolic rate. Fourth, increased physical activity inherent to the DOW method likely contributes to weight loss based on the energy expenditure required to move away from the rotation. Fifth, loss of body weight could also be due to bacterial invasion as severe systemic infection is observed after DOW-induced sleep deprivation (Everson and Toth, 2000). Sixth, brown adipose tissue (BAT) mediated thermoregulation in response to heat loss and increased sympathetic tone would be expected to contribute to negative energy balance in rodents that are sleep deprived using the DOW method. Unlike in rodents, BAT-induced thermogenesis is not the predominant thermoregulatory mechanism in humans, which highlights an additional difference between rodent and human sleep deprivation studies. Finally, it is controversial whether the thermoregulatory function of sleep is important only for small animals with a high thermoregulatory load. Rechtschaffen and Bergmann (1995) suggested that reduced or suspended body temperature regulation (during sleep) was necessary to maintain long-term and effective thermoregulatory system and for this reason total sleep deprivation may result in severe derangements in thermoregulation and hence weight loss. Though the above mechanisms have been suggested to explain weight loss observed after sleep deprivation induced by the DOW method, it is possible that other mechanisms or a combination of several may precipitate weight loss and ultimately death. It is important to note that when sleep deprivation by this method is stopped and rats are allowed sleep recovery time, many of these physiological derangements disappear.

In a similar approach, selective deprivation of REM sleep using the “flower-pot” method also results in hyperphagia, increased metabolic rate and body weight loss (Koban et al., 2005, 2006). The reduction in body weight may again be due to stress associated with confinement to a small platform during sleep deprivation. With a different methodology for sleep deprivation referred to as gentle handling for 5 h, rats had increased feeding behavior, but body weight was not measured (reviewed in Laoposky et al., 2008b). The duration of sleep deprivation is another contrasting feature between sleep deprivation studies in rodents and humans. In a majority of studies, rats are subjected to chronic sleep deprivation for prolonged periods, unlike modern day human sleep restriction, which is characterized by daily opportunities to sleep. A recent study in rodents mimicked human sleep restriction and measured its effect on metabolic rate. In that study, rats that were sleep restricted using a motor driven walking wheel for 18h per day for ten days exhibited a positive energy balance compared to total sleep-deprived rats (Caron and Stephenson, 2010). This demonstrates that unlike total sleep deprivation, sleep restriction (with daily sleep opportunities) increases body weight, which would be most similar to the human condition. In support of this idea, selective deprivation of SWS impaired glucose tolerance (Tasali et al., 2008) and sleep restriction altered glucose metabolism, decreased energy expenditure and increased hunger, appetite, food intake and body weight in humans (Knutson et al., 2007; Pejovic et al., 2010). Likewise, REM sleep deprivation for 72 h increased food intake, body weight gain and preference for carbohydrate rich food in rats (Bhanot et al., 1989). The presence of low energy expenditure during sleep restriction studies may be due to excessive sleep during the

active phase following sleep restriction since active phase sleep parallels low physical activity. Together these studies suggest that severe sleep deprivation by stressful methods produces weight loss, while less severe sleep deprivation or sleep restriction promotes weight gain, reconciling the apparently opposing effects on body weight observed between early sleep deprivation studies in rodents and more recent sleep restriction studies in humans.

3. Circadian alterations in obesity

The above studies show an association between body weight and sleep disturbances, but other factors independent of the sleep/wake cycle may contribute to this relationship. Recent studies provide evidence that the circadian Clock system and the food entrained oscillator (FEO) are critical factors regulating both sleep and energy metabolism.

3.1. The Circadian system

The hypothalamic suprachiasmatic nucleus (SCN), the master pacemaker in the brain, and clocks in peripheral tissues together comprise and regulate the circadian system (reviewed in Marcheva et al., 2009; Dibner et al., 2010). The retino-hypothalamic tract (RHT) conveys photic signals to the SCN, which then indirectly project to the subparaventricular zone and the dorsomedial hypothalamus (DMH, also proposed to be the potential food entrained oscillator). The DMH projects to discrete hypothalamic areas important for regulation of the sleep/wake cycle, the stress response, autonomic nervous system control, feeding and energy expenditure (Saper, 2006; Gooley et al., 2006). The generation of circadian rhythms in response to SCN-light entrainment are dependent on the cyclic expression of circadian clock genes. (Lowrey and Takahashi, 2004). Two key transcription factors, circadian locomotor output cycles kaput (Clock) and brain muscle-arnt-like-factor-1 (Bmal1), direct the SCN and are considered key components of the circadian system (Marcheva et al., 2009). Hence these permissive genes modulate the activity of the light:dark cycle entrained-SCN and downstream nuclei. This in turn underlies the maintenance and coordination of most behavioral and physiological rhythms including the sleep/wake cycle, locomotion, feeding behavior, hormone release and gene transcription as well as the coordination of central and peripheral clocks (Horikawa et al., 2005; Marcheva et al., 2009; reviewed in Laposky et al., 2008b; Mistlberger, 2011), which demonstrates how the circadian system integrates behavioral and metabolic signals.

Timing of the sleep/wake cycle is ultimately the master output of the circadian clock as all other behaviors are dependent on whether an organism is asleep or awake (Laposky, 2008b). Critical involvement of key clock genes such as Clock and Bmal1 in maintaining sleep architecture and quality further supports the role of the circadian system in sleep regulation (Laposky et al., 2005; Naylor et al., 2000; Easton et al., 2004; Moore, 2007).

Recent studies indicate that the molecular circadian clock also modulates energy metabolism. The clock genes are expressed not only in brain but also in numerous peripheral tissues involved in metabolism such as liver, adipose tissue and pancreas (Kohsaka and Bass, 2007; Marcheva et al., 2009; Reppert and Weaver, 2002). Furthermore, clock mutant mice are obese, exhibit hypoinsulinemia, hyperglycemia, hyperleptinemia, hyperlipidemia and have alterations in energy metabolism, feeding, locomotor activity and sleep/wake rhythms (Turek et al., 2005; Rudic et al., 2004; Lamia et al., 2008). Moreover, hepatic clock gene machinery modulates circadian oscillations of rate-limiting enzymes involved in energy metabolism resulting in hepatic glucose storage or release into the circulation in response to hyper- and hypoglycemia (e.g. during feeding and fasting, respectively) (Marcheva, 2010; Stokkan et al., 2001; Hara et al., 2001b; Lamia et al., 2008). Supporting this, liver specific Bmal1 mutant mice exhibit rapid weight gain, higher body fat and,

glucose intolerance (Bunger et al., 2000; Lamia et al., 2008). Like hepatocytes, clock genes modulate insulin secretion by pancreatic beta cells during periods of feeding to maintain glucose homeostasis (Marcheva et al., 2010). Pancreas-specific Bmal1 knockout mice had elevated plasma glucose levels, impaired glucose tolerance and insulin secretion despite normal circadian activity, feeding rhythms and body weight (Laposky, 2008b; Marcheva et al., 2009; Marcheva et al., 2010). Studies have also shown that the Clock:Bmal1 transcription complex can directly modulate the activity and control the expression of genes critical for energy metabolism (Laposky et al., 2008b; Marcheva et al., 2009; Oishi et al., 2005a, b; Fontaine and Staels, 2007). These studies support the plausibility that disruption of the peripheral or central circadian clock may predispose one to obesity and other metabolic disorders independent of sleep abnormalities, and that sleep alterations observed in obesity may be secondary to altered circadian function.

3.2. The food entrained oscillator (FEO)

Analysis of endogenous wakefulness, feeding and physical activity patterns indicates that these behaviors align with the period that precedes food availability in schedule-fed or food-restricted rodents. This behavioral activity or “food anticipatory activity” (FAA; Damiola et al., 2000; Mistlberger, 1994; Stokkan et al., 2001) also mirrors the temporal pattern of body temperature, cortisol release and DMH-c-fos expression among schedule-fed and food restricted nocturnal rodents (Saper 2006, Gooley 2006). This type of restricted feeding also reset peripheral tissue clock gene oscillations (reviewed in Lamia et al., 2008; Marcheva et al., 2009; Mistlberger, 2011). Despite that a specific location for the FEO has yet to be determined, studies suggest that the regulation of FAA is external to the SCN since food entrainment persists in SCN-lesioned animals (Horikawa et al., 2005; Hara et al., 2001b; Mistlberger, 1994). Early studies were inconclusive as to whether the FEO was confined to a single brain area or distributed between the central nervous system and periphery (Davidson et al., 2003; Gooley et al., 2006; Saper, 2006; Landry et al., 2006; Landry et al 2007; Mistlberger, 2011). More recent studies, suggest a diffuse FEO location across clock-containing tissues since peripheral and central clock gene oscillations can be entrained to scheduled feeding. This implies that integration of clock gene rhythms by a network of tissues may function as the FEO to generate FAA (Mistlberger, 2011).

Existence of FAA demonstrates that a range of factors including behaviors (sleep deprivation, feeding), neuro-humoral signals (adiposity, glucose, leptin, activity of autonomic nervous system), and peripheral processes control central and peripheral oscillator activity. In support of this idea, sleep deprivation under controlled levels of stress and activity shifts the circadian clock (Antle et al., 2000) and caloric restriction alters the circadian system response to light entrainment (reviewed in Laposky et al., 2008b). Furthermore, rodents fed with daily palatable snacks have food anticipatory behavior and elevated clock gene expression in brain reward circuits, and food restricted Zucker obese rats have heightened food anticipatory behavior (Mistlberger and Marchant, 1999; Mistlberger, 2011).

Early studies highlight the role of FEO in metabolism and suggest that entrainment of peripheral clocks by the fasting-feeding cycle may allow clock-containing tissues to anticipate daily food consumption to optimize food ingestion, metabolism, energy utilization and storage (Lamia et al., 2008). This suggestion is further supported by a precisely regulated alignment of sleep and activity behaviors with the normally timed feeding and metabolic functions. Thus, disruption of peripheral circadian clocks or misalignment in timing of sleep/activity, clock regulated metabolic rhythms or central and peripheral clocks may disrupt the feeding and metabolic cycle to induce obesity. Thus, sleep disturbances or dietary manipulations may indirectly lead to weight gain by altering the functioning of FEO.

Overall, these findings suggest that an altered circadian system or FEO may affect metabolism independent of sleep. Furthermore, sleep deprivation alters electrical activity in SCN neurons, indicating that sleep effects on metabolism may occur indirectly through SCN-mediated alternations in circadian rhythmicity (Marcheva et al., 2009). Since timing of food can entrain behavioral and physiological rhythms, defects in food entrainment or daily feeding rhythms may impair circadian organization of physiological outputs and metabolism, which may lead to diurnal hyperphagia and obesity independent of disturbed sleep homeostasis (Gangwisch, 2009; Kohsaka et al., 2007). In support of this idea, nighttime illumination desynchronizes food intake timing and locomotor activity and leads to metabolic disorders (Fonken et al., 2010). Animals and humans typically show enhanced food intake during the active phase, but animals exposed to continuous light or humans with night eating syndrome or night-shift workers eat more during the typical rest phase and gain significantly more weight (Fonken et al., 2010; Stunkard and Lu, 2010; Karlsson et al., 2001). Likewise, mice restricted and fed a high-fat diet during the resting phase have greater body weight and food intake (Arble et al., 2009). Thus altered feeding rhythms may continuously reset the FEO to in turn lead to metabolic derangements independent of sleep.

4. Rodent models of obesity and obesity resistance: sleep/wake changes

Obesity is a multi-factorial condition in humans and characteristics of obesity are common in animal models. Some models show deficient leptin or orexin signaling similar to obese individuals and narcoleptic patients (Beck et al., 2001; Laposky et al., 2006; Megirian et al., 1998; Sanchez-Alavez et al., 2007; Tschop and Heiman, 2001; Zhang et al., 2007), but unlike human obesity, obesity in several models results from a single gene deficiency. Sleep architecture in these animal models resemble the abnormalities observed in human obesity (excessive sleep, specifically during the active phase; sleep fragmentation; decreased REM sleep during the resting phase). Studying these models may permit evaluation of drugs and lifestyle interventions to improve sleep quality and treat development of excess body weight in humans.

In the next section, we review sleep profiles of common rodent models used to study obesity and metabolic syndrome. We include the following models to illustrate the critical interaction between sleep and obesity: obesity resistant (OR) or diet resistant (DR) rats, obese Zucker rats, leptin-deficient (ob/ob) and resistant (db/db) mice, diet-induced obese mice, obese spontaneously hypertensive rats, lean high capacity runner rats (HCR), narcoleptic mice, prostaglandin receptor deficient (EP3R^{-/-}) mice, ubiquitin knockout mice (Ubb^{-/-}) and cafeteria diet fed rats.

4.1. Obesity resistant (OR) rats

Two decades ago Levin et al (Levin et al., 1989) showed that approximately one third of out-bred Sprague–Dawley (SD) rats developed diet-induced obesity when exposed to high-fat diet, whereas about one third showed resistance to diet-induced obesity and remained lean. These diet-induced obese (DIO) or obesity prone (OP), and diet-resistant (DR) or obesity resistant (OR) rats, have been selectively bred for generations, and exhibit divergent body weight gain profiles despite similar or unequal caloric intake (Madsen et al., 2010; Patterson et al., 2008). Due to selective breeding, OR rats did not gain excess weight even when fed high-fat diet. Thus these rats are an excellent model to study the neural underpinning of obesity resistance. In contrast to the other rodent models, the OP/OR model is a polygenic model and more likely to reflect human obesity than the single-gene knockout animals like ubiquitin knockout (Ubb^{-/-}) mice and narcoleptic mice, or animals with spontaneous mutations in a single genes, like leptin-deficient (ob/ob) mice. Early studies showed changes in monoamine functioning and later differences were found in leptin and ghrelin regulation in OR rats (Levin, 1995; Levin et al., 2003). Our studies suggest that

enhanced orexin function may be a prime determinant of the OR rat phenotype (Kotz et al., 2008; Mavanji et al., 2010; Teske et al., 2008; Teske et al., 2006), since our previous work showed greater spontaneous physical activity (SPA, which was enhanced by orexin), orexin sensitivity and orexin receptor (OXR) mRNA in several brain regions of OR rats compared with obese animals (Kotz et al., 2008; Mavanji et al., 2010; Teske et al., 2008; Teske et al., 2006).

We hypothesized that obesity resistance would be associated with better sleep quality (less sleep fragmentation and sleep during the active period) and thus we monitored sleep/wake states in OR and SD rats. We used SD rats as controls for the sleep/wake studies as SD rats were more obesity-susceptible than OP rats. Our results showed that OR rats spent significantly more time in wakefulness and less time in SWS compared with SD rats during the dark phase and during the 24 h recording period (Mavanji et al., 2010). Although time spent in REM sleep during the 24 h period was similar between groups, OR rats spent significantly more time in REM sleep during the light phase and less time in REM sleep during the dark phase, which suggested that proper amounts of REM sleep during the resting phase were crucial for normal body weight maintenance (Mavanji et al., 2010). Sleep structure analysis showed that differences in time spent in REM, SWS and wake were due to differences in the number and duration of sleep/wake episodes: OR rats had significantly fewer and longer wake, REM sleep and SWS episodes and fewer transitions between sleep stages. Together this demonstrates that OR rats were behaviorally more stable, with a less fragmented sleep/wake cycle, which contrasts with sleep/wake patterns in obese humans and rodent obesity models.

The EEG delta power during SWS reflects the duration of previous sleep debt (Greene and Siegel, 2004) and thus is a measure of sleep drive (Lancel et al., 1992; Mavanji et al., 2010). SWS delta activity may prolong the duration of SWS episodes, and conversely long SWS episode duration decreases sleep drive and delta power (Brunner et al., 1993; Hansen et al., 1998). Poor sleep quality or sleep fragmentation in rodents increases delta power after sleep fragmentation and deprivation (Lancel et al., 1992; McKenna et al., 2007). We compared mean power density in the EEG delta band (0.5–4 Hz) during SWS between OR and SD rats to obtain a measure of sleep drive. EEG slow-wave activity during SWS was lower in OR rats compared with SD rats during active and resting phases and in the overall 24 h recording period. Greater EEG slow-wave activity during resting phase (when sleep pressure is normally low) and dark phase (which is normally associated with more wakefulness and greater pressure for sleep), suggests that SD rats have higher sleep drive. Our regression analysis indicates that body weight was positively correlated with percent time in sleep, SWS, total number of stage transitions and SWS delta power, and was negatively correlated with percent time in wake.

Since orexin modulates the sleep/wake cycle, we also measured orexin-1 receptor (OX1R) and orexin-2 receptor (OX2R) mRNA in sleep regulatory brain sites to analyze mechanisms underlying consolidated sleep/wake cycle in OR rats. Our results showed higher OX2R mRNA in the ventro-lateral preoptic area (VLPO) and dorsal raphe (DR) nucleus in OR rats. The level of OX1R and OX2R mRNA was greater in the locus ceruleus (LC) of OR rats (Mavanji et al., 2010). Orexin application into the VLPO inhibits the sleep active neurons and inhibits sleep, while enhancing wakefulness (Methippara et al., 2000). If elevated OX2R gene expression increased signaling through OX2R, greater wakefulness observed in the OR rats may be due to greater inhibition of VLPO by endogenous orexin levels in response to greater OX2R expression. It was suggested that SWS and REM sleep are suppressed by raphe neurons (Ohno and Sakurai, 2008). Thus, elevated orexin signaling resulting from greater OX2R mRNA may activate the raphe neurons, inhibiting sleep during inappropriate times and stabilizing behavior. Like DR, LC maintains wake, suppresses both SWS and

REM sleep (reviewed in Ohno and Sakurai, 2008). Accordingly, activation of these neurons due to greater OX1R and OX2R expression might have resulted in prolonged wakefulness and inhibition of SWS and REM sleep during normal active periods in OR rats.

Our sleep/wake data in OR rats are consistent with studies in obese humans that lost weight following surgical and non-surgical interventions (Dixon and O'Brien, 2002; Hernandez et al., 2009; Kalra et al., 2005), demonstrating marked improvement in sleep quality, reductions in active period sleep and sleep fragmentation following weight loss. Weight loss also improved psychosocial traits, metabolic factors, and cardiovascular morbidity, which suggests that correction of sleep fragmentation benefits these serious co-morbidities of obesity (Roehrs et al., 1989; Stamatakis and Punjabi, 2010). Since human studies have documented an association between sleep, body weight and physical inactivity, and we showed greater SPA in OR rats, lower weight in OR rats may be due in part to the extra 5% time spent in wakefulness and greater likelihood for more physical activity. *Overall, better sleep quality with lower resting phase sleep fragmentation, lower sleep drive, less sleep and longer wakefulness during the active phase may confer obesity protection in OR rats.*

After documenting improved sleep quality in OR rats, we tested whether chronic partial sleep deprivation increases body weight in these rats by comparing sleep/wake differences and weight gain profiles between three-month old OR and Sprague-Dawley rats subjected to partial sleep deprivation. To do this, we used environmental noise to partially sleep deprive Spague-Dawley and OR rats during the light cycle for 8 hours daily for 9 days. EEG/EMG recordings were scored as wake, SWS and REM sleep in 10-s epochs. The number of episodes in each stage, mean duration of each episode, and number of transitions between stages were noted. We documented increases in body weight following 9 days of partial sleep deprivation. Our results showed that environmental noise reduced sleep and increased time spent in wakefulness compared to baseline recordings without the presence of environmental noise. Partial sleep deprivation altered behavioral stabilization and resulted in sleep fragmentation as demonstrated by significantly increased sleep/wake episode numbers and transitions between sleep/wake states in deprived rats compared to non-deprived rats (Mavanji et al., unpublished observations). Furthermore, the duration of wake episodes were longer and duration of SWS and REM sleep episodes were shorter during the sleep deprivation paradigm. In addition, partially sleep deprived rats gained significantly more weight and had greater food intake during sleep deprivation compared to non-deprived rats (Mavanji et al., unpublished observations). As discussed before, earlier studies demonstrated weight loss following sleep deprivation in rodents (Rechtschaffen et al., 2002). In contrast to our partial sleep deprivation model, stress associated with early sleep deprivation methods, possible enhancement of physical activity and additional factors secondary to the sleep deprivation methods likely caused the weight loss observed in the earlier studies. Thus, moderate sleep deprivation using a less stressful method during the normal rest phase in rats reduced sleep consolidation, increased wake, decreased sleep, and enhanced weight gain, supporting the idea that partial sleep deprivation during the resting phase enhances weight gain even in obesity resistant rats, consistent with human sleep deprivation studies.

Accordingly, with many parallels to the human condition, and weight gain following sleep deprivation, the OR rat appears to be an excellent animal model to study the sleep-loss related neural underpinnings of polygenic obesity and obesity resistance.

4.2. Diet-induced obese mice

The C57BL/6 mouse strain is especially sensitive to high-fat diet (HFD) effects on body weight (Grubb et al., 2009). High-fat diet feeding consistently produced severe obesity, hyperglycemia and hyperinsulinemia in these mice (Black et al., 1998). Because several parallels exist between diet-induced obese mice and human metabolic syndrome, this model

may be a useful model of human obesity. Severity of obesity in HFD-fed mice was dependent on dietary fat level, since body fat was low or high when animals were fed with low or high fat diet, respectively (Black et al., 1998) and C57BL/6 mice remained lean when fed standard low fat laboratory chow (Black et al., 1998; Klempel and Varady, 2011). Sleep recorded in HFD-fed mice revealed significantly less wakefulness and more SWS in both active and rest phases. Like human EDS, the increase in SWS was significantly greater in the dark (active) phase than that observed in the rest phase. Though time spent in REM sleep in HFD-fed mice was not different from baseline despite weight gain in one study (Jenkins et al., 2006), a subsequent study showed increased REM sleep during the dark phase after HFD-induced weight gain (Guan et al., 2008). REM sleep was reduced to baseline levels when the HFD-fed mice returned to standard chow (Guan et al., 2008; Jenkins et al., 2006). Duration of wake episodes also decreased after weight gain, while the number of wake, REM and SWS episodes increased (Guan et al., 2008; Jenkins et al., 2006). The change in episode number and duration indicates lack of behavioral stabilization and intrusion of sleep during active phase, resembling EDS in humans. Similarly, there was a positive correlation between change in active phase sleep time and body weight gain. In a recent study, weight gain significantly reduced wakefulness and increased active period SWS and REM sleep, whereas these changes were all reversed by weight loss (Guan et al., 2008). Thus, in diet-induced obese mice, sleep/wake parameters resemble those observed in human obesity, including excessive sleep and increased REM sleep during the active phase. These changes appear to be reversible with weight loss, resembling the human sleep normalization, and resolution of EDS following weight loss.

Though diet-induced obese mice show alterations in sleep/wake cycle resembling human obesity, the relative effect of the HFD itself or other factors that perpetuate weight gain on the observed changes in sleep/wake states remain unclear. High fat diet feeding altered expression and cycling of circadian clock genes and factors involved in energy balance (Kohsaka et al., 2007) such as rhythm of orexin gene expression and other neuropeptides involved in sleep and energy homeostasis. Moreover, HFD consumption resulted in hyperphagia and increased locomotor activity (Kohsaka et al., 2007; Arble et al., 2009) during the rest phase. Increased feeding behavior during rest phase enhances weight gain (Arble et al., 2009). Accordingly, altered sleep/wake in HFD-fed obese mice may have resulted from the combined effect of altered diurnal feeding and locomotor rhythms or disrupted rhythms of factors that modulate sleep/wake behavior. Based on studies in calorically restricted and schedule-fed rodents, it is clear that changes in food intake and body weight contribute to sleep/wake patterns, but due to the lack of a pair-fed group in these studies, the independent effect of food intake on sleep is unclear.

4.3. Obese Zucker rats

The obese Zucker rat is a commonly used genetic obesity model. These animals are homozygous for the fatty (fa/fa) allele, have a mutation in the leptin receptor, and are obese and exhibit characteristics of human metabolic syndrome (Aleixandre de Artinano and Miguel Castro, 2009; Zucker, 1961). They become noticeably obese by the 3rd to 5th week after birth (Aleixandre de Artinano and Miguel Castro, 2009) and exhibit hyperphagia (Chua et al., 1996b). Food restriction normalizes body weight without affecting body composition and excessive body fat persists in these animals (Cleary et al., 1980). Analysis of sleep/wake parameters in Zucker rats revealed several sleep abnormalities that were also identified in obese humans. Zucker rats had more SWS despite similar REM sleep duration compared with lean rats (Danguir, 1989; Megirian et al., 1998). The sleep/wake cycle was also disrupted and sleep was fragmented. Obese Zucker rats had an abnormal distribution of SWS and REM sleep between active and rest phase and increased total SWS as they spent more time in SWS during the dark phase (Danguir, 1989), which supports the hypothesis

that obesity increases sleepiness and alters the sleep/wake cycle (Danguir, 1989; Vgontzas et al., 2008). Sleep fragmentation was observed primarily during SWS, which may be related to orexin deficiency (Megirian et al., 1998; Zhang et al., 2007) as reductions in orexin gene expression levels have been reported in obese Zucker rats (Cai et al., 2000; Taheri et al., 2001). Thus Zucker rats exhibit hallmarks of human obesity commonly observed, such as greater active phase SWS and sleep fragmentation in the rest cycle (Danguir, 1989; Megirian et al., 1998; van den Berg et al., 2008a) as well as orexin deficiency. Despite these commonalities, obesity in Zucker rats results from a single-gene leptin receptor mutation, unlike the polygenic origin of human obesity, which limits the utility of this model for understanding the relationship between sleep and obesity in humans.

4.4. Leptin-deficient (ob/ob) mice

The ob/ob mouse is a genetic model of leptin deficiency resulting from a spontaneous mutation in the obese (ob) gene, which encodes leptin (Ingalls et al., 1950; Zhang et al., 1994). These ob/ob mice exhibit hyperphagia, profound early-onset obesity, type II diabetes, hyperglycemia, insulin resistance, and dyslipidemia (Zhang et al., 1994), resembling human metabolic dysregulation and morbid obesity. The ob/ob mice also exhibit lower body temperature and locomotor activity compared to wild-types (Pelleymounter et al., 1995). A study characterized the sleep/wake phenotype of obese ob/ob mice (Laposky et al., 2006). The results showed disrupted sleep architecture, behavioral instability and stage shifts in ob/ob mice as indicated by significantly more arousals from sleep and transitions between different vigilance states compared with wild-type mice. Ob/ob mice also had more frequent and shorter sleep/wake bouts, highlighting impaired sleep consolidation. With respect to absolute amounts of sleep; ob/ob mice had more SWS sleep in the 24 h recording period and thus greater total sleep time. Like human EDS, these mice had more active phase SWS than rest phase SWS (Laposky et al., 2006). Also consistent with obese humans, these mice had less REM sleep in the rest phase and more REM sleep in the active phase compared to wild-type mice. Finally, dark cycle SWS delta power was greater in ob/ob mice and they displayed an attenuated diurnal rhythm of SWS delta power across 24 hours, despite normal levels of absolute SWS delta power. This indicates that ob/ob mice were unable to accumulate and dissipate sleep drive normally. In summary, ob/ob mice exhibit sleep alterations similar to those seen in obese humans including more sleep during the active phase, less REM sleep during the resting phase, high sleep fragmentation, and abnormal diurnal rhythms of sleep homeostasis. However, unlike polygenic human obesity, obesity in this model is of monogenic origin.

4.5. Leptin-resistant (Db/db) mice

Db/db mice have a mutation in the leptin receptor (also known as diabetes, db) gene that encodes an isoform of the leptin receptor (Chen et al., 1996; Chua et al., 1996a; Hummel et al., 1966) and are thus a genetic model of obesity and diabetes. A recent study monitored sleep/wake patterns in db/db mice (Laposky et al., 2008a) and found greater sleep time and sleep fragmentation in db/db mice compared to wild-type mice. Normal diurnal rhythmicity of REM sleep, SWS and SWS delta power were attenuated. Greater total sleep time was due to more sleep time in the active phase in db/db mice much like human EDS. The db/db mice exhibited less REM sleep in the rest phase and more REM sleep in the active phase similar to obese humans. Examination of sleep architecture revealed poor sleep quality indicated by more arousals from sleep, more transitions between sleep stages, more bouts of wake and SWS, and shorter bout duration in db/db mice. Furthermore, db/db mice had more bouts of REM sleep in active phase and fewer bouts in resting phase compared to wild-types, which resulted in less REM sleep in the rest phase. These mice also exhibited altered diurnal sleep drive rhythm as indicated by lower SWS delta power levels at light onset, less sharp decline in SWS delta power throughout the light period, and a slower increase in delta power in the

dark period. Hence, sleep in db/db mice resembled sleep abnormalities observed in obese humans characterized by more sleep in the active period, fragmented sleep, less REM sleep in the rest phase, and altered diurnal sleep drive rhythm. However, unlike most obese humans, obesity in this model results from a single defective gene.

4.6. Obese spontaneously hypertensive rat (SHR)

This model of essential hypertension was derived from selectively bred Wistar Kyoto rats with high blood pressure (Okamoto and Aoki, 1963) and has been considered to be a model for abdominal obesity and metabolic syndrome (Kvetnansky et al., 1997; Reaven et al., 1989). These rats have insulin resistance, hypertriacylglycerolaemia and hypertension like most obese humans. Metabolic disturbances observed in the SHR were likely due to the lack of leptin receptors similar to Zucker rats (Aleixandre de Artinano and Miguel Castro, 2009). Like diet-induced obese mice, SHR rats gained significantly more body weight when fed with high-fat/high-sugar diet and became hyperphagic, obese and hyperlipidemic (Miesel et al., 2010; Sato et al., 1996). The SHRs spent more time in SWS sleep in the active phase similar to humans with EDS (Kuo et al., 2004). SHRs also had altered sleep architecture, poor sleep continuity and fragmentation indicated by frequent interruptions in SWS and more transitions from SWS to wake rather than to REM sleep. These observations are consistent with a report suggesting that human sleep fragmentation is a risk factor for obesity and hypertension (Lofaso et al., 1996). Thus, like obese persons, the SHR exhibit more active phase sleep, severe sleep fragmentation, abdominal obesity, insulin resistance and hypertriacylglycerolaemia.

4.7. High Capacity Runner Rats

High and low capacity runner rats (HCR and LCR, respectively) were selectively bred rats for high or low endurance capacity on a treadmill endurance task to study aerobic capacity, energy dynamics and body weight regulation (Koch and Britton, 2001; Wisloff et al., 2005). Unlike lean HCR rats (Koch and Britton, 2001; Novak et al., 2010), obese LCR rats were susceptible to cardiovascular disorders, endothelial dysfunction, insulin resistance, visceral adiposity, hypertriacylglycerolaemia, hypertension and metabolic syndrome (Novak et al., 2010; Wisloff et al., 2005). LCR rats were highly obesity-prone when fed a HFD and gained greater body weight and fat mass (Novak et al., 2010). Like obesity resistant rats, the HCR rats exhibited more locomotor activity compared to LCR rats (Novak et al., 2010). Thus, HCR/LCR rats are a useful model of obesity resistance and sensitivity that mirror characteristics of human adiposity including low aerobic capacity and metabolic derangements (Aleixandre de Artinano and Miguel Castro, 2009; Bohannon et al., 2005). One study measured sleep/wake cycle in this model and showed more time in wakefulness and less time in SWS in LCR rats (Muncey et al., 2010), which contrasts with other obesity models. LCR rats also had poor sleep quality compared to HCR rats, indicated by significantly more state transitions. Low capacity runners also had a shorter average duration of SWS sleep, indicative of fragmented sleep and behavioral instability. These findings in LCR rats are consistent with the direct association between body weight and excessive sleep fragmentation (Muncey et al., 2010). Thus, LCR rats have several parallels to human obesity by exhibiting low physical activity, cardiovascular disorders, insulin resistance, visceral adiposity, hypertriacylglycerolaemia, metabolic syndrome, excessive body weight and low aerobic capacity. However, unlike other obese rats, the LCR rats did not sleep more either during active phase or the 24h recording period and thus obesity may be associated with excessive sleep fragmentation in this model.

4.8. Narcoleptic mice

The neuropeptide orexin (hypocretin), stabilizes behavior, regulates and maintains wakefulness, energy homeostasis and feeding (de Lecea, 2010). Loss of orexin-containing

neurons, orexins or orexin receptors results in narcolepsy in humans and various animal models, characterized by inability to consolidate sleep or wake into long bouts and leads to behavioral instability (Nishino et al., 2000; Willie et al., 2003). Narcoleptic animals had more yet shorter sleep/wake episodes (with the exception for REM) compared to wild-type animals and like obese humans, narcoleptic mice also exhibited longer and more frequent bouts of REM sleep. Together this suggested severely fragmented sleep/wake and excessive REM sleep in narcoleptic mice (Fujiki et al., 2006). Though daily time spent in wake and SWS was not different between narcoleptic and control animals, narcoleptic mice exhibited excessive SWS in the active phase, as observed in human EDS (Fujiki et al., 2006). Narcoleptic animals may be a model of metabolic syndrome and obesity, as these animals had greater body weight compared to control animals despite reduced feeding and drinking behavior (Fujiki et al., 2006; Hara et al., 2001; Hara et al., 2005; Willie et al., 2001; Zhang et al., 2007). These paradoxical effects were mainly due to reduced locomotion and hence reduced energy expenditure (Hara et al., 2001; Zhang et al., 2007), which parallels observations in transgenic mice lacking orexin-containing neurons (ataxin-3) (Zhang et al., 2007). The ataxin-3 mice had lower locomotion and energy expenditure due to lack of long wake bouts during active phase and were phenotypically, similar to humans with narcolepsy as they exhibited behavioral arrests, premature entry into REM sleep, excessive sleep during active phase, poorly consolidated sleep patterns, and late-onset obesity despite eating less than control littermates (Zhang et al., 2007). Orexin knockout mice were obese and exhibited narcolepsy-like sleep characteristics (Chemelli et al., 1999; Fujiki et al., 2006), which indicates that orexins rather than their co-expressing factors (dynorphin, glutamate) play a critical role in energy balance. Together, these results underscore the critical role of orexin-containing neurons in regulating vigilance states and energy homeostasis and highlight that parallels between obese humans and narcoleptic models. Despite these parallels, narcolepsy is rare and represents one form of human obesity, which contrasts the multifactorial nature typical of human obesity. Finally, despite that obese humans and narcoleptic mice both move less than their lean counterparts, narcoleptic animals are not hyperphagic, which contrasts with human obesity.

4.9. EP3R^{-/-} mice

Mice with a null mutation in the EP3 prostaglandin receptor (EP3R^{-/-} mice) are unable to respond to prostaglandin stimulation and are a model of obesity. These mice were hyperphagic, more physically active (Sanchez-Alavez et al., 2007) and had greater energy intake during the resting phase (light cycle) that might have contribute to the obese phenotype (Fonken et al., 2010). Interestingly, this pattern of increased motor activity and feeding behavior in the rest phase mimics human night eating syndrome and obesity (Stunkard and Lu, 2010). The EP3R^{-/-} mice had impaired glucose tolerance, decreased insulin sensitivity, greater glucose, leptin, insulin, hepatic weight and fat in several depots, which mimics cardinal features of obesity and metabolic syndrome in humans. That EP3R^{-/-} mice gained more body weight and fat mass despite greater physical activity than wild-types suggests that energy intake due to hyperphagia was greater than the energy expenditure. Brown fat was similar between EP3R^{-/-} mice and wild-types, however, the inability to activate brown fat thermogenesis due to lack of the EP3R also likely contributed to body weight gain differences.

Given the prominent role of prostaglandin in sleep regulation and presence of EP3R in the raphe nuclei and locus coeruleus, it is not surprising that EP3R^{-/-} mice have abnormal sleep. Like other obese phenotypes, sleep abnormalities in these mice included the inability to consolidate sleep in the rest period and hence increased sleep fragmentation in the rest phase. Greater sleep fragmentation parallels wakefulness and feeding, coupled with motor activity in the EP3R^{-/-} mice compared with wild-type litter mates. The EP3R^{-/-} mice had

unstable sleep and woke up more easily than controls, similar to sleep fragmentation in humans and other rodent obesity models. The altered sleep/wake regulation in these mice highlights the role of sleep in obesity pathophysiology and the critical role of prostaglandin in sleep regulation (Arble et al., 2009; Sanchez-Alavez et al., 2007). Overall, EP3R^{-/-} mice appear to be a good animal model of obesity that mimics human night eating syndrome and sleep/wake fragmentation observed in obese humans. The limitation of this model is that obesity in EP3R^{-/-} mice is monogenic in origin, unlike human obesity. Moreover, these animals had increased physical activity (measured by telemetry) during the rest phase, unlike humans and many other animal models of obesity that had reduced locomotion.

4.10. Ubiquitin knockout (Ubb^{-/-}) mice

Ubiquitin (Ubb) is essential for cell signaling, cellular functions, protein degradation, transcription, DNA repair and survival. A recent study showed that mice that lacked one of two polyubiquitin genes had low hypothalamic Ubb levels and adult-onset obesity (Ryu et al., 2010; Ryu et al., 2008). Unlike other models, Ubb^{-/-} mice had greater fat mass but less fat-free mass, which resulted in similar body weight compared to wild-types. Consistent with their inability to fully compensate after deprivation-induced feeding, the Ubb^{-/-} mice had disrupted metabolic rate, fewer neurons in the hypothalamic arcuate nucleus, lower orexigenic-NPY and AGRP mRNA as well as higher anorectic-POMC mRNA levels (Ryu et al., 2010; Ryu et al., 2008). A recent study showed that the Ubb^{-/-} mice had lower energy expenditure and moved less in the dark (active) phase even before the onset of obesity (Ryu et al., 2010). Lack of Ubb also resulted in neuro-degeneration in the arcuate nucleus and reactive gliosis in the hypothalamus and other brain areas. Sleep homeostasis was also disrupted in Ubb^{-/-} obese mice. Knockout mice had more SWS and more yet shorter wake episodes than control animals in active phase despite similar sleep/wake in the rest phase (Ryu et al., 2010). Hence, sleep patterns in the knockout mice mimicked that seen in human EDS since both had fragmented sleep and lacked behavioral stabilization. Knockout mice also had disrupted SWS homeostasis since knockout mice had greater sleep deprivation-induced SWS delta power, but failed to show a rebound increase in sleep. Sleep abnormalities and metabolic disturbances in Ubb^{-/-} mice also resembled narcoleptic orexin knockout mice, which exhibited fragmented sleep patterns, excessive active period sleep, reduced physical activity, energy expenditure, and obesity. However, unlike most human obese subjects, REM sleep is normal in the Ubb^{-/-} mice (Ryu et al., 2010) and the obesity in these animals is monogenic in origin.

4.11. Cafeteria diet-fed rats

Rodents fed a mixed high-energy “cafeteria diet” comprised of bread, chocolate, vegetable shortening and shortbread cookies were hyperphagic, obese (Danguir, 1987, Rothwell and Stock, 1979) and had sleep abnormalities. Induction of dietary obesity by a highly palatable diet is perhaps the most relevant animal model to development of human obesity (Sclafani and Springer, 1976). In one study, when fed a cafeteria diet for 14 weeks, rats gained more than 100 g of body weight compared to chow-fed rats (Geiger et al., 2009). Sleep/wake studies showed that time spent in SWS and REM sleep was greater in cafeteria diet fed rats compared to control diet fed rats (Danguir, 1987; Hansen et al., 1998). In these rats time spent in REM sleep was increased only during the rest phase unlike obese narcoleptics. Though SWS was increased during both the light and dark phases, increased SWS during the dark phase mimics EDS in human obese patients. However, cafeteria diet-fed rats had longer SWS episodes, which contrasts with sleep fragmentation observed in human obesity and other rodent models (Hansen et al., 1998). These rats also showed lower EEG slow-wave activity, which indicated altered sleep homeostasis. When the diet pattern was normalized, SWS and REM sleep returned to normal levels within 3 days. These studies suggest a role of increasing sleep in the development of obesity in rats (Danguir, 1987).

Overall, this model mimics the sleep changes observed in human obesity such as increased sleep during the normal active period, greater body weight and food intake. However, while cafeteria diet fed rats exhibited altered sleep homeostasis and EDS, this model lacked sleep fragmentation, a key feature of sleep pattern in human obesity.

5. Potential mechanisms linking sleep disturbances and obesity

The above animal studies document the association between poor sleep quality and development of obesity, while good sleep quality is a common characteristic of obesity resistance and lean phenotypes (Table 1). Though these studies link sleep quality to excessive body weight gain, the mechanisms underlying the co-existence of sleep alterations with obesity are not understood. In the following section, we briefly discuss potential mechanisms linking sleep and obesity.

Previous studies highlight the involvement of leptin and orexin in the relationship between sleep and obesity. A mutation in the leptin receptor or deficient production of leptin is the basis for the obese phenotype in some animal models (Aleixandre de Artinano and Miguel Castro, 2009). Abnormally high leptin levels are common in human obesity (Considine et al., 1996). A small set of people who lack leptin are severely obese and leptin replacement in these subjects ameliorates obesity (Farooqi et al., 1999), however, it is unclear whether there is an effect of leptin on sleep/wake patterns. Pharmacological studies showed increase in SWS and decrease in REM sleep following leptin administration in sated animals, but, there was no effect of leptin in food deprived animals (Sinton et al., 1999). However, as discussed above, leptin deficient and resistant mice sleep more than wild-types, pointing to a role for leptin in the complex interaction between sleep, energy status and obesity.

The neuropeptide orexin (hypocretin) is integral to normal regulation of sleep/wake states and energy homeostasis (de Lecea, 2010). This is most profoundly demonstrated by the loss of orexin-containing neurons or orexin receptors, which results in the sleep disorder narcolepsy and obesity in humans and various animal models (Lin et al., 1999; Willie et al., 2003). Consistent with this idea, lower orexin levels have been observed in obese subjects and various animal models of obesity (Adam et al., 2002; Baranowska et al., 2005; Beck et al., 2001; Bronsky et al., 2007; Kok et al., 2003; Mondal et al., 2002; Stricker-Krongrad et al., 2002). Narcoleptic humans and animals also exhibited alterations in energy homeostasis and gained weight, despite reduced food intake, which underscored the importance of sleep in the development of obesity (Honda et al., 1986; Poli et al., 2009; Schuld et al., 2000). Narcoleptics also presented with EDS, sleep onset REM periods, cataplexy, and fragmented sleep, which further supported a role for orexin in sleep/wake regulation. In contrast to orexin deficiency, orexin over expression consolidated sleep wake states and prevented weight gain in mice (Funato et al., 2009) and daily orexin treatment decreased weight gain in rats (Novak and Levine, 2009). Orexin also stimulated spontaneous physical activity and energy expenditure (Hagan et al., 1999; Lubkin and Stricker-Krongrad, 1998). As physical activity enhances sleep quality (Blanco-Centurion and Shiromani, 2006), it is possible that lack of orexin or insufficient orexin signaling and resultant low physical activity promotes the co-existence of poor sleep quality and obesity. Thus, orexin appears to be a potential link that bridges metabolism, sleep and obesity.

The role of the circadian clock in sleep regulation has been well established (Cajochen et al., 2010). Recently it was suggested that an altered circadian clock and sleep quality may directly affect neuro-endocrine systems involved in the regulation of energy balance resulting in obesity. For example, altered sleep quality affected the sympathetic nervous system, HPA axis, brain metabolism and also altered appetite by affecting leptin and ghrelin levels (Magee et al., 2010). Collectively these changes lead to an imbalance between energy

intake and energy expenditure that lead to obesity (Kohsaka and Bass, 2007; Kohsaka et al., 2005; Spiegel, 2004; Taheri et al., 2004), (Figure 1). Alternately, poor quality sleep in the rest phase may promote excessive sleep, fatigue, physical inactivity and low energy expenditure in the active phase, which would perpetuate body weight gain. Lack of physical activity would further deteriorate sleep quality. This may culminate in a vicious cycle with poor sleep quality and low physical activity perpetuating obesity and weight gain in turn further deteriorating sleep quality (Figure 1).

Recent studies suggest that tumor necrosis factor –alpha (TNF-alpha) may be an additional potential mechanism that links obesity and poor sleep quality. Tumor necrosis factor –alpha enhanced sleep, and obesity often co-exists with low degree inflammation and high expression of inflammatory markers like TNF-alpha (Vgontzas et al., 2008). Thus, high TNF-alpha may promote sleepiness commonly observed among obese persons. In support of this idea, neutralization of TNF-alpha reduced EDS in obese men (Vgontzas et al., 2008), which further suggested that TNF-alpha might mediate the relationship between sleep quality and obesity. The above findings highlight potential mechanisms that regulate metabolism and the sleep/wake cycle, however, the role of other neuromodulators including serotonin, norepinephrine, histamine, acetylcholine, prostaglandins, adenosine and sleep modulating peptides cannot be ruled out. Overall, many neuromodulators that regulate energy homeostasis have a profound influence on sleep–wake states, which highlights the integration between mechanisms modulating sleep and metabolism.

6. Concluding remarks

Accumulating evidence shows a reciprocal modulatory relationship between body energy status and the sleep/wake cycle. For example, consumption of high-fat diets (Jenkins et al., 2006, Wells et al., 1997) and food restriction have opposite effects on sleep (Danguir and Nicolaidis, 1979) and the development of diet-, genetic- or environmentally-induced obesity parallels increased SWS, specifically during the active phase. Similarly, human studies show increased sleep in severe forms of obesity (Vorona et al., 2005). On the other hand, sleep loss is followed by metabolic disturbances in humans and animals (Rechtschaffen and Bergmann, 1995; Spiegel et al., 2004). Based on the above observations insufficient sleep may lead to metabolic disturbances and it is also possible that altered metabolism (and/or development of obesity) independently affects sleep-wake regulation.

Polygenic obesity is most relevant to human obesity, and thus to gain understanding of the relationship between sleep and obesity, sleep behavior analysis in polygenic animal models will be most useful. It is important to understand whether abnormal sleep causes obesity or whether obesity is antecedent to abnormal sleep. It is also crucial to emphasize the role of independent components of sleep quality like sleep fragmentation as factor(s) influencing body weight gain. Recent human studies show a bimodal relationship between sleep and obesity, and some of these studies with objective measurement of sleep also show long sleep duration and sleep fragmentation associated with obesity. Since polygenic rat models and experimenter-induced animal models of obesity are available, it would be advantageous to fully utilize these models to characterize sleep changes relating to obesity and obesity-resistant phenotypes. In addition, genetically modified mouse models may provide insight into the pathophysiological significance of specific molecular mechanisms for sleep and obesity interactions. Furthermore, dietary manipulations that induce obesity could aid in the definition of novel mechanisms for body weight-induced changes in sleep regulation. Finally, definition of sleep and metabolic endpoints in well-characterized obesity models with sleep alterations could provide the basis for preclinical pharmacologic intervention studies.

Typical sleep disturbances observed in obese humans such as EDS, sleep fragmentation, altered REM sleep, and disrupted diurnal rhythm of sleep have been noted in obese animal models (Table 1). Altered sleep is linked to functional changes in the complex neural systems that regulate both body weight and the sleep/wake cycle, ranging from brainstem to fronto-cortical regions. Our earlier studies suggest that the orexin system may be a causal link between sleep disturbances and metabolism. For example, we demonstrated resistance to weight gain, greater spontaneous physical activity, orexin sensitivity and orexin receptor mRNA in the rostral lateral hypothalamus of OR rats compared with obese rats (Kotz et al., 2008, Teske et al., 2006; Teske et al., 2008). Recently, we also showed consolidated sleep/wake behavior and increased brain orexin receptor expression in sleep/wake regulatory areas in OR rats (Mavanji et al., 2010). Together, these studies underscore the prominent role of orexin in the integration of sleep and metabolism at the central level and suggest that sleep alterations observed in obese and OR animals may be associated with defective orexin function.

As described earlier, we showed that environmental noise results in sleep deprivation accompanied by increased body weight and hyperphagia, mirroring human sleep deprivation while contrasting with earlier sleep deprivation studies in rodents using stressful methods such as DOW. Duration of sleep deprivation is another contrast between studies in rats and humans. In the majority of studies, rats were subjected to chronic sleep deprivation for prolonged periods, unlike modern day human sleep restriction, which is characterized by daily opportunities to sleep. Thus, our rodent model of partial sleep deprivation underscores the relevance and significance of using a less stressful method of sleep deprivation with daily opportunity to sleep to appropriately model the effects of human sleep restriction on metabolism.

It is crucial to conduct new experiments focusing on the behavior, pharmacology and biochemistry of sleep and obesity to understand the association between vigilance states and obesity. If the role of sleep quality is proven to be a risk factor for obesity, sleep quality enhancement can be a clinical tool for the treatment of obese individuals.

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Highlights

- Obesity in humans is associated with disturbances in sleep and sleep homeostasis.
- We examined sleep-obesity associations in rodent models of obesity.
- These models exhibit most of the key sleep disturbances observed in obese humans.
- Thus, rodent obesity models also support an association between sleep and obesity.
- Improving sleep quality may be a clinical tool to treat obese individuals.

Figure 1. Schematic representation of the possible mechanisms linking sleep quality and obesity (HPA axis, Hypothalamic-Pituitary-Adrenal axis).

Table 1

Sleep/wake characteristics in rodent obesity models

Animal Model	24h Wake time	Active period sleep	Sleep fragmentation	Sleep/wake bouts	Diurnal rhythm of S/W states	Transition between states	Rest period REM sleep
Obese Zucker rat (Danguir, 1989, Megirian et al., 1998)	↓	↑	↑	Not measured	Altered	Not measured	No change
Diet-induced obese mice (Guan et al., 2008, Jenkins et al., 2006)	↓	↑	No change	↑In number ↓In duration of Wake	Not measured	Not measured	No change
Spontaneously hypertensive rat (Kuo et al., 2004)	↓	↑	Not measured	Not measured	Not measured	↑	No change
Low Capacity Runner Rats (Muncey et al., 2010)	↑	↑	↑	↓In duration of SWS	Not measured	↑	No change
Narcoleptic mice (Zhang et al., 2007, Fujiki et al., 2006)	No change	↑	↑	↑In number ↓In duration	Altered	Not measured	No change
EP3R ^{-/-} mice (Sanchez-Alavez et al., 2007)	No change	No change	↑	Not measured	Not measured	↑	No change
Ubiquitin knockout (Ubb ^{-/-}) mice (Ryu et al., 2008, 2010)	No change	↑	↑	↑In number	Altered	Not measured	No change
Cafeteria diet-fed rats (Danguir, 1987; Hansen et al., 1998)	No change	↑	No change	↑In duration of SWS	Altered	Not measured	↓
Ob/ob mice (Laposky et al., 2006)	No change	↑	↑	↑In number ↓In duration	Altered	↑	↓
Db/db mice (Laposky et al., 2008)	No change	↑	↑	↑In number ↓In duration	Altered	↑	↓
OR rats (Mavanji et al., 2010)	↑	↓	↓	↑In duration ↓In number	Improved, with low sleep drive	↓	↑

OR rats. Obesity resistant rats; S/W states, Sleep/wake states; ↑ increased; ↓ decreased.