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Sleep disorders, obesity, and aging: the role of orexin

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Abstract

The hypothalamic neuropeptides orexin A and B (hypocretin 1 and 2) are important homeostatic mediators of central control of energy metabolism and maintenance of sleep/wake states. Dysregulation or loss of orexin signaling has been linked to narcolepsy, obesity, and age-related disorders. In this review, we present an overview of our current understanding of orexin function, focusing on sleep disorders, energy balance, and aging, in both rodents and humans. We first discuss animal models used in studies of obesity and sleep, including loss of function using transgenic or viral-mediated approaches, gain of function models using exogenous delivery of orexin receptor agonist, and naturally-occurring models in which orexin responsiveness varies by individual. We next explore rodent models of orexin in aging, presenting evidence that orexin loss contributes to age-related changes in sleep and energy balance. In the next section, we focus on clinical importance of orexin in human obesity, sleep, and aging. We include discussion of orexin loss in narcolepsy and potential importance of orexin in insomnia, correlations between animal and human studies of age-related decline, and evidence for orexin involvement in age-related changes in cognitive performance. Finally, we present a summary of recent studies of orexin in neurodegenerative disease. We conclude that orexin acts as an integrative homeostatic signal

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influencing numerous brain regions, and that this pivotal role results in potential dysregulation of multiple physiological processes when orexin signaling is disrupted or lost.

Keywords

orexin; hypocretin; obesity; sleep; aging; energy balance

1. INTRODUCTION

Identified by two independent groups, the endogenous neuropeptides, orexin A and B (also known as hypocretin 1 and 2), and their associated G-protein coupled orexin type 1 and 2 receptors (OX1R and OX2R, respectively, also known as hypocretin receptor type 1 and 2), constitute the multi-functional central orexin system (de Lecea et al., 1998; Sakurai et al., 1998). Orexin synthesis is relatively confined to neurons in the lateral-posterior-perifornical hypothalamus, while orexin receptors are widely distributed in a brain site-specific manner (Marcus et al., 2001; Trivedi et al., 1998). Unlike orexin synthesizing neurons, orexin fibers are ubiquitous, extensively innervating peripheral and central targets (Date et al., 1999; España et al., 2005; Nixon and Smale, 2007; Peyron et al., 1998). Due to the extensive terminal field, central orexin signaling is well positioned to integrate and orchestrate multiple physiological processes such as arousal, whole-body energy metabolism, reward seeking, autonomic function, and ventilatory control (Burdakov et al., 2013; de Lecea and Huerta, 2014; Karnani and Burdakov, 2011; Kotz et al., 2012; Mahler et al., 2012). Aberrant orexin function has been associated with several pathophysiologies, such as obesity, narcolepsy and other sleep disorders, as well as the occurrence and severity of age-related disorders (Fadel et al., 2013). Here we briefly review the literature documenting the role of orexin in sleep disorders, energy balance, and aging. We discuss animal models and clinical studies, highlighting how alterations in central orexin signaling affects body weight, food intake, sleep patterns, and progression of age-related pathologies. We conclude that central orexin signaling is a promising target for pharmacological therapies to alleviate a myriad of disorders.

2. Animal Models

2.1. Rodent models for studying the role of orexin in obesity

Initial behavioral studies suggested that orexin was important in mediating central control of ingestive behavior and energy metabolism (Bray, 2000; Lubkin and Stricker-Krongrad, 1998; Sakurai et al., 1998). These studies showed orexin A had opposite effects on energy balance since exogenous orexin A stimulated hyperphagia and energy expenditure. This is unusual in that most peptides known to stimulate ingestion also inhibit sympathetic activity and thermogenesis, reducing energy expenditure (reviewed in Bray, 2000). Subsequent studies have indicated orexin influences individual propensity for weight gain, and have shown that orexin receptor stimulation results in a net negative energy balance. Rodent models for studying the role of orexin in obesity have been developed and tested, and include genetic gain and loss-of-function models, as well as pharmacologic and outbred models of individual variability.

2.1.1. Loss-of-function—Mice lacking orexin function either through genetic knockout (KO) of the gene encoding orexin or through postnatal ablation using an ataxin toxin develop late onset obesity (Chemelli et al., 1999; Hara et al., 2001; Hara et al., 2005). In both models, food intake and energy expenditure are affected by the absence of orexin function. These animals are hypophagic (eat less), and have substantially reduced energy expenditure, which appears to be primarily due to reductions in physical activity (Hara et al., 2001). Hara et al (Hara et al., 2005) showed important phenotypic differences in deleting orexin function by these two methods: losing the orexin *gene* vs. losing the entire orexin *neuron*. With the latter approach, co-localized neurotransmitters, including dynorphin, cocaine and amphetamine-related transcript, glutamate, neuronal activity-regulated pentraxin, and others are lost, and thus the impact that these neurotransmitters and their projections have on energy balance are also affected. Studies have shown that in the orexin/ataxin-3 model and in orexin gene KO mice, the obesity phenotype depends upon the mouse genetic background, level of knockdown and environment (Fujiki et al., 2006; Hara et al., 2005). While both the KO mice with a mixed or C57Bl/6J genetic background and the orexin/ataxin-3 mice with a C57Bl/6J background are heavier than wild type mice, body weight is similar between mixed background orexin/ataxin-3 mice and wild type mice. Body weights of orexin/ataxin-3 mice are greater than orexin KO mice and the body weight of heterozygote mice on a mixed background is intermediate between that of homozygous knockouts and wild type mice. The latter suggests that severity of obesity increases as orexin function declines. Female mice exhibit a higher level of obesity, potentially indicating greater sensitivity to orexin loss in females (Fujiki et al., 2006). Together, these data suggest that orexin (e.g. vs. other co-localized factors) and genetic background are critical for the obese phenotype on orexin-manipulated animal models (Fujiki et al., 2006; Hara et al., 2005). Injection studies demonstrate that a single intraperitoneal administration of a selective orexin 1 receptor antagonist (SB-334867-A) reduces food intake in both male and female rats (Haynes et al., 2000). Further, the same antagonist delivered chronically into cerebral ventricles of leptin deficient (ob/ob) mice over 14 days reduced body weight gain by reducing food intake (Haynes et al., 2002), although leptin deficient mice have baseline differences in energy regulation, limiting interpretation.

2.1.2. Gain of function—Studies by Yanagisawa and colleagues have demonstrated that orexin overexpression promotes energy expenditure while also reducing food intake and that central administration of an orexin receptor 2 agonist reduced diet-induced obesity (Funato et al., 2009). Reduction in energy expenditure is in agreement with other studies, but reduction in food intake by an orexin agonist is surprising. It is unclear why this discrepancy exists. Nonetheless, transgenic overexpression of orexin and the orexin receptor 2 affords protection from obesity when mice are placed on a high fat diet. Novak et al have shown that daily injection of orexin A into the hypothalamic paraventricular nucleus results in weight loss in rats (Novak and Levine, 2009), and recently, Perez-Leighton et al showed that daily orexin A injections into the rostral lateral hypothalamus reduces fat mass gain in rats on a high fat diet (Perez-Leighton et al., 2012). These studies demonstrate that enhanced orexin signaling, via increase in peptide or in receptor activation, can protect against weight gain.

2.1.3. Individual variability in orexin—Studies by Kotz et al have demonstrated that outbred rats resistant to obesity induced either by diet or age have high gene and protein expression of orexin receptors (Mavanji et al., 2010; Novak et al., 2006; Teske et al., 2006). Studies by Perez-Leighton et al show that individual sensitivity to obesity depends upon the level of gene expression for prepro-orexin: outbred rats with higher levels of the orexin prepro gene are resistant to fat mass gain, whereas those with low levels are sensitive to fat mass gain (Perez-Leighton et al., 2013). In all of these studies, the obesity resistant phenotype aligned with high orexin tone, high levels of physical activity and sleep quality, and high energy expenditure, whereas the obesity prone phenotype aligned with low orexin tone, low physical activity and sleep quality, and low energy expenditure.

Collectively, animal models show that orexin signaling influences propensity for weight gain. While some studies have shown decreased food intake after orexin receptor antagonism, overall, orexin signaling appears to promote a net increase in energy expenditure. Orexin loss of function models commonly exhibit reduced energy expenditure and increased weight gain leading to obesity (Hara et al., 2005), and enhanced orexin signaling or sensitivity to orexin has been shown in multiple selectively-bred and outbred models of obesity resistance in rodents (reviewed in Butterick et al., 2013). Together these findings suggest that orexin tone and responsivity is central for mediating energy expenditure, which has a profound impact on obesity susceptibility.

2.2. Rodent models for studying the role of orexin in sleep disorders

The ability of orexin to promote wakefulness, and to maintain and stabilize behavioral states, underscores the crucial role of the orexin system in regulation of sleep and wakefulness (Brisbare-Roch et al., 2007; Nishino et al., 2000; Willie et al., 2003). Sleep disruption is a common symptom of several central nervous system disorders, and is associated with abnormal orexin function (Dauvilliers et al., 2003). While the strongest evidence supporting the role of orexin in sleep are data showing that the sleep disorder narcolepsy is caused by disrupted orexin signaling (Chemelli et al., 1999; Chen et al., 2009; Nishino et al., 2000), it is unclear how orexin contributes to other disorders of sleep and wakefulness. Mechanistic studies in rodent models can elucidate the association between altered orexin function and sleep disorders.

Narcolepsy is a rare sleep disorder characterized by excessive daytime sleepiness, short sleep latency, and sleep onset REM periods (American Academy of Sleep Medicine, 2014). Narcolepsy may present with or without cataplexy, or a brief loss of muscle tone with retained consciousness, and associated features may include disturbed nocturnal sleep, sleep paralysis, and or hypnagogic hallucinations (American Academy of Sleep Medicine, 2014; Dauvilliers et al., 2007). A deficit in the orexin system is the primary pathophysiology of this disease (Fronczek et al., 2009). Rodent models of narcolepsy that either lack the orexin gene, orexin neurons, or orexin receptors have been studied to elucidate the orexin role in this debilitating sleep disorder (reviewed by de Lecea et al., 2002; Zhang et al., 2006).

2.2.1. Genetic Models—The orexin KO mouse, produced by targeted replacement of the first orexin gene exon, was the first rodent model of orexin-deficient narcolepsy

characterized (Chemelli et al., 1999). These orexin null mice exhibit behavioral arrests in the dark (active) phase that are strikingly similar to catalepsy in human narcolepsy (Chemelli et al., 1999). Chemelli et al referred to these arrests as “narcoleptic attacks” instead of cataplexy, as they were unable to determine if consciousness was preserved, a critical feature of cataplexy. Orexin null mice all displayed sleep onset REM periods, fragmented sleep, and greater REM sleep during the dark (active) phase. Development of the orexin/ataxin-3 mouse and rat, rodent models with a selective and postnatal ablation of orexin neurons, soon followed (Beuckmann et al., 2004; Hara et al., 2001; Zhang et al., 2007a). These models more closely mimic the postnatal loss of orexin neurons in human narcolepsy (Peyron et al., 2000). In these animals, orexin-containing neurons were undetectable in 15-week-old orexin/ataxin-3 mice (Hara et al., 2001), reduced by 75% as early as 4 weeks in the orexin/ataxin-3 rats (Zhang et al., 2007a), and absent by 17 weeks (Beuckmann et al., 2004). Similar to sleep observed in the orexin null mice, orexin/ataxin-3 mice and rats have fragmented sleep and increased wake to REM sleep transitions (Beuckmann et al., 2004; Hara et al., 2001; Zhang et al., 2007a; Zhang et al., 2007b). However, unlike orexin null mice, orexin/ataxin-3 mice and rats spend less time in REM sleep in the light phase (Beuckmann et al., 2004; Hara et al., 2001). While narcolepsy in humans is associated with the absence of hypothalamic orexin, the significance of orexin receptors was highlighted by dog studies of narcolepsy, caused by a mutation in the canine OX2R gene (Lin et al., 1999). Shortly thereafter, abnormal sleep patterns in single or double orexin receptor KO mice were reported (Willie et al., 2003; Willie et al., 2001). Mice lacking OX2R display several abnormalities similar to human narcolepsy (Willie et al., 2001), yet the behavioral phenotype of OX2R KO mice appears less severe than orexin null mice, as OX2R KO mice display less frequent sleep onset REM periods, less sleep/wake fragmentation, and spend less total time in REM sleep (Chemelli et al., 2000; Chemelli et al., 1999; Willie et al., 2003; Willie et al., 2001). A comparison of mice lacking OX1R or OX2R revealed differential regulation of orexin receptor subtypes on REM sleep and NREM sleep suppressed by orexin A (Mieda et al., 2011). Stimulation of OX2R was more efficacious at reducing REM sleep compared to OX1R, while both orexin receptor subtypes were equally efficacious at suppressing NREM sleep. Double orexin receptor KO mice display sleep/wake disturbances most similar to human narcolepsy (Willie et al., 2001), while OX1R KO mice have no overt behavioral abnormalities except for increased sleep/wake fragmentation (Kisanuki et al., 2000). Blocking orexin signaling at both receptors may thus be necessary to mimic symptomology in human narcolepsy. Overall, the sleep patterns of rodent models with insufficient orexin signaling resemble human narcolepsy, indicating that future genetic and neurochemical studies with these models may provide important clues to the etiology and treatment of many debilitating human sleep disorders.

2.2.2. Non-genetic models—In addition to the genetic models described above, *in vivo* non-genetic approaches have been used to study the role of orexin in sleep/wake regulation. Lateral hypothalamic administration of orexin B conjugated to the neurotoxin saporin eliminated up to 90% of orexin neurons (Gerashchenko et al., 2003b) inducing narcolepsy-like behavior (Gerashchenko et al., 2003a; Gerashchenko et al., 2001; Gerashchenko et al., 2003b), and mimicking the orexin neuron loss and sleep disturbances of narcolepsy. In another study, microdialysis perfusion of OX2R antisense into the pontine reticular

formation for three days increased REM sleep and cataplexy (Thakkar et al., 1999). Likewise, Chen et al showed that perifornical hypothalamic infusion of short interfering RNA (siRNA) specific to prepro-orexin mRNA significantly (59%) suppressed prepro-orexin mRNA, decreased the number of orexin-positive neurons, induced cataplexy-like episodes, and increased REM sleep during the dark phase (Chen et al., 2006). The latter two studies provide evidence for the diurnal gating of REM sleep by orexins, suggesting that targeting central orexin pathways for treating sleep disorders is promising, as the effects of OX2R antisense and prepro-orexin RNA interference were reversed 4–6 days post injection. Unlike previous studies interrogating orexin function alone, stimulation of orexin neuron function by optogenetics (de Lecea and Huerta, 2014) reduced latency to wakefulness and increased sleep/wake transitions (Adamantidis et al., 2007), the latter requiring noradrenergic signaling in the locus coeruleus (Carter et al., 2012). Thus, promising non-genetic models are available to further probe the role of orexin in the regulation of sleep and sleep disorders. In summary, the discovery of orexin marks a milestone in sleep research. A thorough understanding of the orexin system and its effect on specific sleep regulatory brain sites aids development of orexin analogues and small molecule orexin receptor antagonists, as treatments for hypersomnias and insomnias, respectively.

2.3. Rodent models for studying orexin and aging

Orexin moderates physiological processes that undergo age-related change, implying that aberrant orexin signaling contributes to altered sleep/wake and metabolism during aging. Age-related decline in the orexin system has been widely documented in animals, and parallels physiological alterations in body weight regulation and sleep during aging (Downs et al., 2007; Kappeler et al., 2003; Kessler et al., 2011; Kotz et al., 2005; Porkka-Heiskanen et al., 2004a; Porkka-Heiskanen et al., 2004b; Sawai et al., 2010; Terao et al., 2002; Zhang et al., 2002, 2005a). A significant decline in orexin immunopositive neurons has been observed as early as eight months in rats (Sawai et al., 2010), which is near the age at which a time-dependent change was also observed in mice (Brownell and Conti, 2010). Aging also influences the diurnal expression of orexin A in cerebrospinal fluid (CSF). While the overall diurnal pattern is consistent between young and aged mice (Yoshida et al., 2001; Zeitzer et al., 2003), others showed that orexin A in CSF is lower in aged 21-month old Fischer rats during the light and dark cycle (Desarnaud et al., 2004). Age-related morphological change in orexin neurons has been noted in aged cats (Zhang et al., 2002) and rats (Zhang et al., 2007a) that had ‘spot-like’ structures absent in younger animals. These orexin immunopositive ‘spot-like’ structures were identified as enlarged axon terminals by electron microscopy (Zhang et al., 2005b). Zhang et al concluded that aging associated morphological changes alters orexin signaling and may underlie “aged-related function of the orexin system” (Zhang et al., 2005b). Age-dependent effects on the orexin system appear to be modified by gender and species. In contrast to other species, distribution of orexin cell bodies, number of orexin neurons, and serum orexin B concentrations are similar between aged and young rhesus macaques (Downs et al., 2007), and there is no age-dependent effect on preproorexin (Terao et al., 2002) or orexin A (Lin et al., 2002) in C57BL/6J mice. In mice, while orexin immunopositive neurons decline with increasing age, males retain more neurons compared to age-matched female C57Bl/6J mice from 6–24 months of age (Brownell and Conti, 2010). In light of studies suggesting functional heterogeneity of orexin

neurons, the pattern of loss, rather than the total number of neurons lost, may also be important in determining the behavioral effect of orexin neuron loss in aging. Several studies suggest that a medial-lateral division exists in orexin neurons, with medially- and dorsomedially-located neurons projecting to arousal regions, while those located laterally play a role in food intake (España et al., 2005; Fadel et al., 2002). Dysfunctional orexin signaling related to age-associated declines in orexin neuron number, gene expression, orexin peptide levels or receptors or the pattern of loss may underlie age-related change in metabolic and sleep-related behavior.

Age-dependent neuroanatomical and morphological changes in the orexin system parallel behavioral and physiological processes including sleep (Morairty et al., 2011; Porkka-Heiskanen et al., 2004a), metabolism (Martone et al., 2013; Poehlman and Horton, 1990), insulin sensitivity (Tsuneki et al., 2008), hemodynamics (Hirota et al., 2003), and cognition (Stanley and Fadel, 2012). The functional significance of senescence on the hypothalamic orexin system is exemplified in a rodent model of healthy aging. Lou C/JaLL rats have higher hypothalamic preproorexin mRNA and lower body weight than Wistar rats, and normal food intake at 24 months of age (Kappeler et al., 2004). Likewise, in BRASTO brain-specific *Sirt1*-overexpressing transgenic mice, there is a youthful metabolic and behavioral phenotype coinciding with enhanced OX2R promoter activity. Aged BRASTO mice have higher physical activity, body temperature, oxygen consumption, sleep quality, and skeletal muscle mitochondrial function relative to aged-matched controls (Satoh et al., 2010; Satoh et al., 2013). Moreover, aged-BRASTO mice have greater OX2R mRNA in dorsomedial hypothalamus (Satoh et al., 2010; Satoh et al., 2013), and knockdown of Sirt1 or OX2R abrogates BRASTO heightened physical activity and body temperature. Consistent with Sirt1 enhancement of OX2R promoter activity in cultured cells (Satoh et al., 2010), Satoh and colleagues further demonstrated that a combination of Sirt1 and Nk2 homeobox 1 enhances OX2R promoter activity, suggesting that enhanced Sirt1-mediated OX2R underlies the prolonged lifespan and youthful behavior of aged-BRASTO mice.

Studies suggest a dysfunctional orexin system potentiates adiposity gain during aging. Senescent animals display reduced food intake or age-related anorexia, which has been defined as declines in caloric intake or appetitive drive with increasing age (Akimoto and Miyasaka, 2010; Kmiec, 2006, 2011; Martone et al., 2013). In addition to reduced *ad libitum* food intake, aged animals display diminished hyperphagic response to central orexin A infusion (Akimoto and Miyasaka, 2010; Kotz et al., 2005; Takano et al., 2004) with a concomitant decline in orexin neuron activity (Kotz et al., 2005). While reduced appetite seems discordant with body weight gain, orexin dysfunction during aging has a more profound effect on energy expenditure. Reductions in age-related orexin drive would elicit a more robust reduction in energy expenditure than energy intake, promoting body weight gain despite reduced consumption.

Synonymous with reduced food intake, enhanced satiety in aged animals may be a response to lower energy expenditure, reduced physical activity, and thermoregulatory dysfunction during aging (Blatteis, 2012; Holowatz and Kenney, 2010). It is widely appreciated that reduced physical activity parallels advancing age in humans and other species (Kmiec et al., 2013; Manini, 2010), which would be expected to contribute to reduce daily energy

expenditure. We and others have demonstrated the robust contribution of orexin signaling to physical activity and energy expenditure in young rodents (reviewed in Kotz et al., 2012; Lubkin and Stricker-Krongrad, 1998; Novak and Levine, 2007). Based on the promotion of physical activity, temperature and energy expenditure by orexin, it is plausible that during aging, reduced orexin-stimulated physical activity would reduce daily physical activity, which in turn would be expected to reduce physical activity-associated energy expenditure. Reductions in resting metabolism likely contributes to lower total energy expenditure with advancing age (Elia et al., 2000). Reductions in resting metabolism related to sarcopenia due to low physical activity would also contribute to reductions in total energy expenditure. Thermoregulation may be augmented as a consequence of sarcopenia (Kenney and Buskirk, 1995). It is clear that orexin participates in diminished thermogenic capacity in rodents. Brown adipocytes within interscapular brown adipose tissue from aged mice have fewer multilocular cells and thus are morphologically more similar to white adipocytes. This morphological change parallels deficient thermoregulation and a lower ability to mobilize intracellular fuel reserves from brown adipocytes (Sellayah and Sikder, 2014). That orexin A treatment reverses the morphological and functional consequences of aged interscapular brown adipose tissue, indicated by greater uncoupling protein one mRNA, increased cold tolerance, and weight loss, supports the hypothesis that orexin dysfunction with advancing age augments energy expenditure to promote obesity during aging (Sellayah and Sikder, 2014). Moreover, orexin influences autonomic function including sympathetic outflow, implicating that age-related orexin neurodegeneration may contribute to reduced cutaneous thermoregulatory blood flow during advancing age. Together these age-related alterations in physical activity, energy expenditure (resting and physical activity-related), and thermoregulation would be expected to promote the reductions in total daily energy expenditure and increase adiposity gain observed in aged humans.

3. Clinical implications

The contribution of central orexin signaling to human pathophysiology is well recognized. Abnormalities in orexin signaling pathways underlie the pathophysiology of sleep disorders (Baumann and Bassetti, 2005a, b; Cao and Guilleminault, 2011; Dyken and Yamada, 2005; Malhotra and Kushida, 2013; Mignot, 2004; Overeem et al., 2001; Ritchie et al., 2010; Tafti et al., 2005; Taheri et al., 2002; Wisor and Kilduff, 2005; Zeitzer, 2013) such as narcolepsy (Nishino et al., 2000; Peyron et al., 2000; Thannickal et al., 2000) and may contribute to posttraumatic hypersomnia or excessive daytime sleepiness due to traumatic brain injury (Baumann, 2012; Baumann et al., 2009), post traumatic stress disorder (Strawn et al., 2010), or obstructive sleep apnea (Ahmed et al., 2012; Wang et al., 2013). Insufficient central orexin signaling has also been associated with other medical conditions (Mignot et al., 2002; Vankova et al., 2003) such as obesity (Van Cauter and Knutson, 2008), age-related anorexia (Kmiec et al., 2013), multiple system atrophy (Benarroch et al., 2007), neurological disorders (Fronczek et al., 2009), Parkinson’s disease (Fronczek et al., 2007; Thannickal et al., 2007; Wienecke et al., 2012), and Alzheimer’s disease (Slats et al., 2013). Since symptomology may not parallel CSF orexin levels (Dauvilliers et al., 2003; Martinez-Rodriguez et al., 2003; Nishino et al., 2003; Ripley et al., 2001) and low orexin levels and aberrant sleep have been reported in other medical conditions, it is difficult to verify

causality (reviewed by Mignot, 2004; Mignot et al., 2002; Taheri et al., 2002). Hence, determining the contribution of abnormal orexin signaling to human pathophysiology may lead to improved therapeutic avenues.

3.1. Orexin and obesity in humans

The earliest descriptions of narcolepsy highlighted elevated BMI, body weight, and central obesity (Dahmen et al., 2001; Kok et al., 2003; Nishino et al., 2001; Schuld et al., 2000) and underscored the critical link between orexin dysfunction, sleep, and obesity. Whereas narcolepsy is caused by dramatic loss of orexin signaling, evidence suggests that milder perturbations of the orexin system may disrupt the normal orexinergic gating of sleep/wake state transitions and thus contribute to poor sleep quality. In addition, orexin deficient narcoleptic patients are more obese compared to narcoleptic patients with normal CSF orexin levels (Nishino et al., 2001). Weight reduction has been shown to increase plasma orexin in adolescents (Bronsky et al., 2007), suggesting that increased adiposity might result in reduced orexin signaling. The relationship between orexin and obesity is complex, and in many cases it is difficult to determine whether factors such as physical activity level, sleep quality, or circulating orexin levels are a consequence of or a causal factor for development of obesity.

3.2. Orexin and sleep in humans

The sleep disorder narcolepsy best exemplifies the clinical manifestations of dysfunctional central orexin signaling. Common symptoms of narcolepsy include excessive daytime sleepiness and abnormal manifestations of REM sleep noted during polysomnography, refreshing naps, mean sleep latency less than or equal to eight minutes, and two or more sleep onset REM periods on a mean sleep latency test. Associated features may include sleep paralysis, hypnagogic hallucinations, or autonomic behavior. Narcolepsy, also referred to as hypocretin deficiency syndrome and narcolepsy with or without cataplexy, has recently been subcategorized to narcolepsy type I and II in the third edition of the International Classification of Sleep Disorders (American Academy of Sleep Medicine, 2014). Absent or low levels (≤ 110 pg/ml or < 1/3 of mean values obtained in normal subjects with the same standardized assay (American Academy of Sleep Medicine, 2014)) of orexin in CSF is the hallmark feature of narcolepsy type I. When cataplexy is absent yet CSF orexin is normal or unknown, individuals are diagnosed with narcolepsy type II (American Academy of Sleep Medicine, 2014).

Narcolepsy type I is caused by a deficiency in orexin signaling due to loss of orexin neurons (reviewed in Kornum et al., 2011; Mignot, 2004; Overeem et al., 2001; Siegel, 1999; Siegel and Boehmer, 2006; Taheri et al., 2002). Strong association between narcolepsy and the human leukotype antigen DRD2 or DQB1*0602 implies autoimmune destruction of orexin neurons (reviewed by De la Herran-Arita and Garcia-Garcia, 2014; Fontana et al., 2010; Kornum et al., 2011; Lin et al., 2001; Mignot, 2004; Singh et al., 2013). Homozygosity for DQB1*0602 or heterozygosity for DQB1*0602/0301 is highly associated with narcolepsy (Hong et al., 2002; Hor et al., 2010; Kornum et al., 2011; Mignot et al., 1997; Mignot et al., 2001). However, some patients with narcolepsy present with normal orexin levels or are negative for human leukotype antigen DR2 or DQB1*0602, the percentage of the population

positive for the DQB1*602 far exceeds the narcolepsy prevalence (Taheri et al., 2002) and there is a low rate of concordance for narcolepsy in monozygotic twins (Mignot, 1998), indicating that, as with other auto-immune disorders, gene-environment interactions (Kroeger and de Lecea, 2009; Taheri et al., 2002) and non-genetic factors contribute to narcolepsy pathogenesis (Ritchie et al., 2010). In rare cases, mutations or polymorphisms in the preproorexin gene or the orexin two receptor parallel a positive diagnosis (Dong et al., 2013; Peyron et al., 2000).

Experience with deficient orexin in narcolepsy led to the question of whether too much orexin activity might be responsible for insomnia. One formulation of this concept labels the problem of insomnia as hyperarousal (Bonnet and Arand, 2010; Riemann et al., 2010), driven by excess orexin. These ideas formed the basis for development of orexin antagonist medications for treatment of insomnia, and the first of these medications has been approved by the FDA. Suvorexant is a dual receptor antagonist, thereby blocking both orexin receptors. In clinical trials, suvorexant has improved sleep efficiency in short term and long term treatment (Herring et al., 2012; Michelson et al., 2014). There have been concerns that orexin antagonism might lead to narcoleptic symptoms, but no significant symptoms were observed in trials thus far (Herring et al., 2012; Michelson et al., 2014). Orexin antagonists therefore appear to be a promising avenue for treatment of an otherwise resistant condition, insomnia.

3.3. Orexin and aging in humans

Reduced energy expenditure, reduced food intake, and weight loss occur in elderly humans (Kmiec et al., 2013; Manini, 2010). This ‘anorexia of aging’ has been attributed to reduction in number or in sensitivity to a number of appetite-regulating peptides, including orexin (Kmiec et al., 2013). As summarized above, animal models show that orexin loss occurs during aging, and this loss is specific to orexin neurons rather than due to general age-related neurodegeneration (Kessler et al., 2011), although at least one study in primates has shown no correlation between age and orexin neuron number (Downs et al., 2007). Overall, the strength of the animal models suggest a similar loss of orexin would occur in aged humans. Outside of disease models, change in orexin neuron number with age has only recently been directly examined in humans (Hunt et al., 2014). This study showed a 23% decrease in orexin neuron number from infancy to late adulthood, with a 10% decline occurring between early and late adulthood (Hunt et al., 2014). Aside from this study, and those utilizing brain tissue analysis from persons with narcolepsy, studies in humans have relied mainly on plasma or CSF levels of orexin. Somewhat paradoxically, human plasma orexin levels have been shown to increase with aging, although the relationship between plasma and brain orexin is undefined, and plasma orexin likely relates more to peripheral than central orexin action. In humans, plasma orexin level correlates with age, with lower levels in subjects under 40, and higher levels among those aged 60 or more (Matsumura et al., 2002). In women, plasma orexin increases significantly during menopause (El-Sedeek et al., 2010). Among menopausal women, those receiving hormone replacement therapy have lower levels of plasma orexin than those receiving placebo (El-Sedeek et al., 2010). Plasma orexin is known to increase after weight loss in obese children and in lean and obese adults (Bronsky et al., 2007; Heinonen et al., 2005; Komaki et al., 2001), suggesting that increase

in plasma orexin is not inconsistent with orexin involvement in age-related weight loss. However, increased plasma orexin is difficult to explain if age-related loss of orexin neurons occurs in humans. Studies in rodents suggest orexin receptors are also lost during aging (Porkka-Heiskanen et al., 2004a; Terao et al., 2002). If the same is true in humans, reduction in orexin receptors may result in greater production of peptide to overcome reduced sensitivity, or to increased unbound peptide, ultimately leading to higher levels of orexin in plasma. Plasma orexin level may also inaccurately reflect actual number of orexin neurons. In both rodents and humans, substantial loss of orexin neurons (50–70%) is required before significant decrease in CSF levels of orexin are evident (Fronczek et al., 2007; Gerashchenko et al., 2003b). Plasma orexin may be even more variable, as animal studies have shown orexin is produced in the enteric nervous system of the gut as well as in brain (Kirchgessner, 2002; Kirchgessner and Liu, 1999). However, a recent study failed to observe orexin-producing neurons in human gut tissue (Baumann et al., 2008), and no studies have examined whether orexin-producing neurons outside of the central nervous system decline with aging.

Aging is also associated with a number of changes affecting sleep, energy homeostasis, and cognition. While few studies have specifically investigated aging and orexin in humans, data from these and from animal studies support that a decline in either orexin neurons or orexin sensitivity in older individuals contributes to at least some aspects of these age-related changes. First, the most salient recognized function of orexins is promotion of arousal and stabilization of the sleep/wake cycle. Age-related decrease in orexin would thus be expected to negatively impact sleep duration and sleep quality, and incidence of sleep disturbance, sleep disorders, and insomnia do increase with age in humans (Drake et al., 2003; Wimmer et al., 2013). Second, orexin has been linked to promotion of energy expenditure in rodents (Kotz et al., 2008; Kotz et al., 2002; Kotz et al., 2006; Lubkin and Stricker-Krongrad, 1998; Teske et al., 2006; Thorpe and Kotz, 2005). Average daily energy expenditure in humans is known to increase throughout childhood, peaking at adolescence, and decreasing around 100–160 kCal per day each decade in women and men, respectively, throughout the remainder of life (Manini, 2010). This decline in daily energy expenditure with aging parallels reductions in physical activity observed in humans and animal models with orexin deficiencies (Hara et al., 2001; Nishino et al., 2001). Finally, orexin is known to affect performance in cognitive tests of spatial and working memory (Akbari et al., 2007; Deadwyler et al., 2007). Age-related decline in cognitive abilities are common in older adults, with incidence of diagnosis increasing from 4 to 36% between the ages of 65 and 85 (Black and Rush, 2002). In addition to normal decline in orexin during aging, orexin loss is a component of several progressive neurodegenerative diseases, including Alzheimer's, Parkinson's, and Huntington's diseases (Fronczek et al., 2007; Fronczek et al., 2012; Petersen et al., 2005; Thannickal et al., 2007). Sleep disturbances and cognitive deficits are known comorbidities of these diseases. While the underlying cause of orexin loss in these disorders is unknown, it is possible that some aspect of these neurodegenerative disease processes greatly accelerate the normal age-related reduction in orexin neurons. It is increasingly evident that sleep, activity and cognition are interconnected (Horne, 2013), as age-related disturbances in one component also affect the others. It is plausible that orexin loss contributes to cognitive decline in both normal aging and in neurodegenerative disease,

whether through direct involvement of orexin in cognitive tasks, or indirectly through effects on sleep and activity.

Many prior studies have shown that orexin neurons may be important mediators of cognitive performance. Orexin neurons appear to synapse directly on basal forebrain cholinergic neurons important in cognition (Castillo-Ruiz et al., 2010; Fadel et al., 2005; Frederick-Duus et al., 2007), and orexin appears to mediate long-term potentiation in the dentate gyrus of the hippocampus (Akbari et al., 2011). Prior work utilizing operant tasks shows that supplementing orexin might affect cognitive processes (Choi et al., 2010; Sharf et al., 2010; Thorpe et al., 2005). Orexin treatment improves performance in progressive ratio, fixed ratio, and delayed matching to sample tasks in rodents and primates (Choi et al., 2010; Deadwyler et al., 2007; Thorpe et al., 2005). Further, several lines of evidence support that blocking orexin action can impair cognition. The selective orexin 1 receptor antagonist SB-334867 impairs performance in progressive and variable ratio operant testing (Sharf et al., 2010), decreases performance in an attentional task in rats (Boschen et al., 2009), and impairs performance in passive avoidance and spatial memory tests (Akbari et al., 2008; Akbari et al., 2006, 2007). The wake-inducing drug modafinil, which activates orexin neurons, improves attention in rats (Morgan et al., 2007; Scammell et al., 2000), and the stimulant nicotine appears to act in part through activation of orexin neurons projecting to the basal forebrain and thalamus (Pasumarthi and Fadel, 2008). Interestingly, modafinil, nicotine, and acetylcholine all affect or are affected by orexin signaling in cognition, and modafinil, nicotine and acetylcholinesterase inhibitors are routinely used as cognitive enhancers in humans (Husain and Mehta, 2011).

While some degree of decline is to be expected with age, the relative severity of impairments caused by physical and cognitive impairments can often lead to reduced independence and quality of life by interfering with the ability to perform daily tasks (Black and Rush, 2002; Huh et al., 2011; Wang et al., 2006). If orexin loss during aging does contribute to age-related decline in sleep, energy expenditure, and cognition, therapies aimed at increasing orexin signaling may prove beneficial for the elderly by positively impacting all of these factors. There appears to be a synergistic relationship between decline in physical activity and cognitive performance in older adults, in that changes in one measure predict future changes in the other. Studies examining measures of physical ability and cognitive function have shown both that early identification of reduced cognitive function correlates with future decline in physical ability (Black and Rush, 2002; Huh et al., 2011), and that physical impairments are also indicators of future cognitive decline (Black and Rush, 2002; Wang et al., 2006). There is ample evidence that interventions that increase physical activity might improve cognitive function in all age groups (Colcombe et al., 2004; Davis et al., 2011; Etnier et al., 2006). In one study of older adults, aerobic exercise intervention improved cognitive performance in an executive attentional task and in functional MRI measures of cortical plasticity (Colcombe et al., 2004). A meta-regression of 37 studies on cognition and physical activity also showed a positive correlation between cognitive ability and physical activity (Etnier et al., 2006). Interestingly, this study found no correlation between aerobic fitness and cognitive function, suggesting that the increase in overall physical activity rather than in vigorous aerobic exercise is important in maintaining cognitive ability. If true, this implies that that loss of spontaneous physical activity inducing

agents, such as orexin, might contribute to cognitive decline, and that treatments that increase spontaneous physical activity during aging might also exert a protective effect against cognitive decline. Increased spontaneous physical activity could encourage better health through physical movement, potentially counteracting normal age-related increases in sedentary behavior (Manini, 2010), and through the cognitive feedback stimulated by ambulation, especially if performed in an engaging environment (Horne, 2013).

3.4. Orexin in neurodegenerative disease

As discussed above, loss of orexin neurons and sleep disturbances are known comorbidities of several neurodegenerative diseases, including Parkinson's (PD) and Alzheimer's disease (AD) (Fronczek et al., 2007; Fronczek et al., 2012; Petersen et al., 2005; Thannickal et al., 2007). While many studies have focused on the importance of orexin loss in disease-related sleep disturbances, several recent reports suggest orexin may also play a role in some aspects of neurodegenerative disease pathogenesis. Orexin receptor 2 polymorphisms have been identified as a potential risk factor for development of AD (Gallone et al., 2014), however in another study loss of orexin neurons in narcoleptics failed to alter AD risk (Scammell et al., 2012). With respect to PD, the incidence of prior narcolepsy diagnosis was five times higher than expected in PD patients (Christine et al., 2012), suggesting that narcolepsy or narcolepsy treatments might influence development of PD. However, drugs aimed at treating PD might selectively damage orexin neurons (Katsuki and Michinaga, 2012), making interpretation of narcolepsy-PD links difficult. Evidence strongly links development of AD and PD with oxidative stress and mitochondrial dysfunction in the brain (Agostinho et al., 2010; Ferreiro et al., 2012; Niranjan, 2013). In recent *in vitro* and *in vivo* studies, we and others have shown that orexin is neuroprotective, reducing neuronal damage caused by ischemia or oxidative insult in hypothalamic, hippocampal, and cortical tissue (Butterick et al., 2012; Sokolowska et al., 2012; Yuan et al., 2011). While the mechanism is not fully defined, orexin appears to increase resistance to oxidative stress by upregulation of hypoxia-inducible factor 1 alpha (HIF-1α) (Butterick et al., 2013; Feng et al., 2014; Sikder and Kodadek, 2007; Yuan et al., 2011). HIF-1α is a transcription factor that alters mitochondrial activity by increasing ATP production through oxidative phosphorylation, and affects expression of transferrin, a gene important in regulating iron metabolism in the brain (Semenza, 2001; Weinreb et al., 2013). Increased oxidative stress and dysfunction in brain iron metabolism are associated with etiology of both AD and PD (Loeffler et al., 1995; Nestrasil et al., 2010; Niranjan, 2013; Weinreb et al., 2013). With respect to PD, HIF-1α activation has been proposed as a potential therapeutic treatment (Weinreb et al., 2013), and orexin has recently been shown to protect against the Parkinsonian neurotoxin 1-methyl-4-phenylpyridinium (MPP+)-induced toxicity through induction of HIF-1α in a dopamine-producing neuronal cell line (Feng et al., 2014). Taken as a whole, these results suggest that orexin might protect against development of neurodegenerative disease, and that orexin loss in AD and PD might exacerbate disease progression by increasing susceptibility to oxidative damage. While promising, the overall significance of these findings are currently unclear, and other studies have shown contradictory conclusions. For example, orexin has been positively linked to increased amyloid-β (Aβ) accumulation in a mouse model of AD (Kang et al., 2009). Sleep deprivation in this study caused an increase in amyloid plaque formation, while a dual orexin receptor antagonist decreased Aβ accumulation. These results suggest

increased orexin signaling could exacerbate rather than protect against development of AD. A more recent study has shown that while Aβ accumulation is correlated with sleep disturbances in mice, prevention of amyloid plaque formation also normalizes sleep/wake cycles (Roh et al., 2012). If orexin loss contributes to disease progression of AD, sleep disruptions due to decreased orexin signaling would be expected even if plaque formation were reduced. The importance of orexin signaling in neurodegenerative disease is potentially promising but unclear at present.

4. CONCLUSION

While our focus here is on the role of orexin in energy metabolism and sleep, it is clear that this multifaceted peptide also influences other physiological processes. Orexin is likely to play an integrative role, coordinating central modulation of sleep and physical activity in the context of energy balance. While uniquely positioned to tie many disparate systems together, this connectivity has a down side. When dysfunction of the orexin system occurs, a great number of regulator and behavioral systems are affected. Because of this confound, it can be difficult to disentangle the effect of orexin on sleep, obesity, or cognition alone, for example, as orexin has been shown to have direct or indirect effects on all three. Despite these difficulties, the influence of orexin on multiple systems also presents the possibility of simplifying therapeutic treatments, as orexin-based therapies might positively impact multiple morbidities. For example, promotion of healthier sleep patterns through enhanced orexin signaling could also lead to reduction in weight and improved cognitive performance, while orexin-based therapies in the elderly designed to increase physical activity may also stabilize sleep patterns. Although orexin clearly represents only one component in the complex regulatory mechanisms underlying aging, obesity, and sleep disorders, there is clear potential benefit of developing orexin-based therapies to alleviate symptoms of these health conditions in humans.

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Highlights

- Central orexin signaling declines with age
- Dysregulation of orexin function is associated with obesity and sleep disorders
- Reduced orexin impacts body weight, sleep, and age-related pathologies
- Orexin effects on sleep and activity may also impact cognitive performance
- Orexin may be a therapeutic target for treatment of multiple age-related disorders