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Energy Expenditure: Role of Orexin

Jennifer A. Teske[*,†] and **Vijayakumar Mavanji**[‡]

[*]Department of Nutritional Sciences, University of Arizona and Southern Arizona VA Health Care System, Tucson, Arizona, USA

[†]Department of Food Science and Nutrition, University of Minnesota, Saint Paul, Minnesota, USA

[‡]Minnesota Obesity Prevention Training Program, School of Public Health, University of Minnesota and Minneapolis VA Health Care System, Minneapolis, Minnesota, USA

Abstract

The orexins/hypocretins are endogenous, modulatory and multifunctional neuropeptides with prominent influence on several physiological processes. The influence of orexins on energy expenditure is highlighted with focus on orexin action on individual components of energy expenditure. As orexin stabilizes and maintains normal states of arousal and the sleep/wake cycle, we also highlight orexin mediation of sleep and how sleep interacts with energy expenditure.

I. Introduction

The hypocretins (hypocretin 1 and 2) are neuropeptides with significant amino acid homology to the secretin/incretin protein family that were described first by de Lecea *et al*. (1998) after their earlier report documented isolation of its precursor, preprohypocretin (Gautvik *et al*., 1996). One month later, Sakurai *et al*. reported identification of the same neuropeptide and associated their two G-protein-coupled receptors, however, referred to the neuropeptides as orexins (orexin A and B, OXA and OXB) due to their observation of hyperphagia after central administration (Sakurai *et al*., 1998). Unlike other neuropeptides, synthesis of the precursor protein, preprohypocretin or prepro-orexin, is confined to discrete regions in the lateral and lateral/perifornical hypothalamus (Gautvik *et al*., 1996). However, orexin protein is ubiquitously expressed in several brain nuclei, in all levels of the central nervous system and within discrete peripheral locations (Chen *et al*., 1999; Cutler *et al*., 1999; Date *et al*., 2000; Nambu *et al*., 1999; Peyron *et al*., 1998). Like orexin protein distribution, orexin receptors (orexin receptor 1 and 2, OX1R and OX2R) are ubiquitously distributed centrally and in discrete peripheral locations (Cluderay *et al*., 2002; Hervieu *et al*., 2001; Johren *et al*., 2001; Marcus *et al*., 2001; Trivedi *et al*., 1998). Of particular note, orexin receptors have been identified in human adipose tissue, and thus targeting orexin receptor-expressing adipose tissue may be an attractive therapeutic tool for metabolism-related pathologies including obesity and diabetes (Digby *et al*., 2006). Despite the near concurrent location of orexin terminals and receptors, OX1R and OX2R are unequally distributed within central and peripheral sites (Cluderay *et al*., 2002; Digby *et al*., 2006; Hervieu *et al*., 2001; Marcus *et al*., 2001; Trivedi *et al*., 1998). For instance, within discrete brain sites such as the locus coeruleus, OX1R is abundantly expressed while OX2R is

relatively void. In contrast, OX2R is highly expressed in the hypothalamic paraventricular nucleus despite null expression of OX1R.

Unlike the expression patterns of prepro-orexin, orexin terminals, and their receptors, less is known regarding the mechanism of action or the intracellular signaling cascades following orexin receptor activation. Regarding the mechanism of action, it is clear that OX1R and OX2R have dissimilar affinity to OXA and OXB such that OX1R has 10-fold greater affinity for OXA relative to OXB, while OX2R appears to have equal affinity for OXA and OXB (Sakurai *et al*., 1998). Although the significance of the dissimilar binding affinity is not readily apparent, the disparate behavioral effects of orexins on energy expenditure-related processes may uncover this physiological relevance. It is also clear that orexin receptor binding can activate various G-alpha subunit proteins including G_q, G_s, and $G_{i/o}$, which increases the complexity of understanding their signaling cascades (Bernard *et al*., 2006; Holmqvist *et al*., 2005; Karteris *et al*., 2001, 2005; Randeva *et al*., 2001). An early report documented that orexin receptor stimulation increased extracellular calcium influx (Ammoun *et al*., 2003; van den Pol *et al*., 1998). Further, neuronal excitation results from activation of L-type calcium channels (Kohlmeier *et al*., 2004), T-type calcium channels (Zhang *et al*., 2009), transient receptor potential cation channel subtypes C1 and C3 (Larsson *et al*., 2005), nonselective cation channels (Yang and Ferguson, 2003), sodium–calcium exchange channel transporter (Burdakov *et al*., 2003; Eriksson *et al*., 2001), as well as the suppression of potassium conductance through G-protein inwardly rectifying potassium channels (Hoang *et al*., 2003; Ivanov and Aston-Jones, 2000). Moreover, orexin stimulates release of glutamate and GABA (van den Pol *et al*., 1998), and stimulation of orexin receptors by OXA and OXB activates p38 mitogen-activated phosphate kinase and extracellular signal-regulated kinases (ERK1/2) (Ammoun *et al*., 2006; Tang *et al*., 2008) by way of multiple signaling mechanisms. Moreover, orexin neurons are energy sensors sensitive to ATP levels (Liu *et al*., 2011) and lactate (Parsons and Hirasawa, 2010) and have been differentially described based on synaptic input and their behavioral, morphological, and electrophysiological profile (Harris *et al*., 2005; Horvath and Gao, 2005). A recent review suggests that orexin neurons function within a local network comprising both coexpressing neurotransmitters within orexin neurons (dynorphin, glutamate, nociceptin/orphanin FQ) as well as neurons devoid of orexin in the lateral hypothalamus that express melanin concentrating hormone, thyrotropin-releasing hormone, corticotropin-releasing hormone, neurotensin, galanin, and GABA (Burt *et al*., 2011). Based on the mirrored distribution between orexin fibers and receptors, the multisynaptic input to the lateral hypothalamus and the local network within orexin neurons, it is not surprising that orexins mediate multiple physiological processes and their role as a physiological integrator could not be made more clear (de Lecea *et al*., 1998; Sakurai *et al*., 1998; Sutcliffe and de Lecea, 2000; Willie *et al*., 2001).

A. Components of energy expenditure

Total energy expenditure can be partitioned into several components (D'Alessio *et al*., 1988; Donahoo *et al*., 2004; Joosen and Westerterp, 2006; Ravussin and Bogardus, 1992; Ravussin *et al*., 1986). However, the relative contribution of each component to total energy expenditure is largely dependent upon the interindividual variability of each component. For

example, energy expenditure from physical activity is the most variable (Ravussin *et al*., 1986). The primary component of total energy expenditure comprising 60–70%, basal metabolism, is defined by the *Webster's Medical Dictionary* as "the turnover of energy in a fasting and resting organism using energy solely to maintain vital cellular activity, respiration, and circulation as measured by the basal metabolic rate" (BMR). Diet-induced thermogenesis, comprising 10–15% of total energy expenditure, is due to the energy required to digest, absorb, and store food. Adaptive thermogenesis or the energy required to thermoregulate and respond to changes in the environmental temperature comprises 10–15% of total energy expenditure. The final and most variable component of total energy expenditure, comprising 6–10%, is due to physical activity thermogenesis or the work derived from all forms of physical activity, postural maintenance, and muscular contraction. This includes both physical activity due to exercise and all other types of physical activity excluding exercise (e.g., spontaneous physical activity or nonexercise activity) (Levine *et al*., 1999; Ravussin *et al*., 1986).

B. Methodological considerations: Energy expenditure and sleep measurements in rodents in the context of obesity research

Orexin modulates food intake, BMR, physical activity, arousal, the sleep/ wake cycle, and hormone regulation and thus has profound influences on energy expenditure. Therefore, it is important to reflect upon common methods currently used to measure energy expenditure, indirect calorimetry. With this method, rodents are placed in a calorimetry chamber and "reference" air of a known percentage of oxygen and carbon dioxide flows into the chamber. The rodent within the calorimetry chamber consumes oxygen and expires carbon dioxide, which combines with the air flowing into the chamber. Through periodic sampling, energy expenditure is calculated based on the difference between the percentage of oxygen and carbon dioxide between the reference and sampled air. Although indirect calorimetry is used to measure total energy expenditure, the method and analysis of energy expenditure are problematic when comparing energy expenditure in rodents within the context of obesity research (Arch *et al*., 2006; Butler and Kozak, 2010; Rauh *et al*., 1990). First, it is currently impossible to partition total energy expenditure into its relative components since an instantaneous change in basal metabolism, physical activity, temperature, or diet-induced thermogenesis cannot be detected in real time. Instead, BMR is commonly considered to be the lowest metabolic rate during the resting phase or derived from a series of metabolic rates with the lowest standard deviation during the resting phase for the animal. Adaptive thermogenesis is considered to be negligible at thermoneutral, which seems germane to consider when comparing energy expenditure between animals of varying body mass, surface area, and volume. Laboratory rodents are commonly housed at temperatures below their thermoneutral (Overton, 2010). Therefore, adaptive thermogenesis and BMR would be greater in rodents with smaller surfaces area to volume ratios. Thus, the derived or calculated BMR may overestimate the true BMR for small animals housed below thermoneutral in an indirect calorimeter, since the calculated BMR will include the energy required for adaptive thermogenesis. Also, while it is possible to measure physical activity and energy expenditure concurrently, physical activity-induced energy expenditure cannot be directly measured. Finally, the metabolic rate during sleep is reported infrequently in indirect calorimetry studies possibly due to the technical difficulties associated with

quantifying and measuring sleep directly. Sleep can be classified broadly into rapid eye movement (REM) sleep and non-rapid eye movement (NREM or slow wave sleep (SWS)) sleep and each has distinct electrographic waveforms in electroencephalogram (EEG) and electromyogram (EMG) signals (Greene and Siegel, 2004). Quantification of sleep and wake first requires continuous recordings of EEG and EMG signals and then requires the EEG/EMG waveforms to be scored and classified as REM sleep, SWS, or wake. Pairing methodology to concurrently time stamp and differentiate sleep and wake states by EEG/EMG recordings and energy expenditure with indirect calorimetry would be an improvement over methods that estimate sleeping metabolic rate. Despite that pairing methodologies are imperfect, as mentioned previously, comparing patterns of sleep, wake, and energy expenditure in parallel will lead to a more accurate estimation of sleeping metabolic rate. This has physiological significance for human obesity given the effect of sleep deprivation on energy expenditure and body mass. Therefore, we focus on orexin modulation of total energy expenditure in addition to the components of energy expenditure including sympathetic outflow, thermo-regulation, physical activity, and sleep; yet acknowledge that many neurotransmitter systems and neuropeptides contribute to the regulation of energy expenditure.

C. Total energy expenditure and metabolic rate

The earliest report of orexin modulation of total energy expenditure was reported shortly after their discovery (Lubkin and Stricker-Krongrad, 1998) and confirmed in later studies (Asakawa *et al*., 2002; Semjonous *et al*., 2009; Wang *et al*., 2001). Mice with cannule directed toward the third ventricle were infused with a single dose of OXA in the light or dark phase among food-deprived or *ad libitum*-fed mice (Lubkin and Stricker-Krongrad, 1998). Interestingly, OXA stimulated metabolic rate and the duration of action was longer after the dark phase injection, suggesting that other components of energy expenditure may have been influenced. It is plausible that energy expenditure due to increased physical activity or sympathetic activity but not diet-induced thermogenesis contributed to the prolonged increase in BMR, since OXA stimulates both physical activity and sympathetic activity and the control-treated mice had greater food intake than the OXA-treated mice. As the site of action for an injectate infused into the brain ventricles is largely unknown, others tested the effects of OXA after infusion into specific brain sites to identify potential sites of action. Wang *et al*. found OXA stimulated whole body oxygen consumption in anesthetized rats after infusion into the arcuate nucleus only (Wang *et al*., 2003). There was no increase after infusion into the locus coeruleus, paraventricular nucleus of thalamus or several hypothalamic nuclei including the medial preoptic area, paraventricular, dorsomedial, ventromedial, and the lateral hypothalamic area. In contrast, in awake freely moving rats, OXA increased whole body energy expenditure after infusion into the hypothalamic paraventricular nucleus (Kiwaki *et al*., 2004; Novak *et al*., 2006) and the lateral hypothalamus (Teske *et al*., 2006). As physical activity would be absent in anesthetized rats, it is plausible that the positive effect of OXA on energy expenditure after infusion in the hypothalamic paraventricular nucleus and lateral hypothalamus in the latter studies may be due in part to increased energy expenditure associated with physical activity.

D. Components of total energy expenditure

1. Sympathetic outflow and thermoregulation—Orexin stimulates thermoregulatory and cardiovascular systems (Ferguson and Samson, 2003; Samson *et al*., 2005; Shirasaka *et al*., 2002; Szekely *et al*., 2002), which would contribute to the increase in basal metabolism following central orexin noted previously. Orexin is largely sympathoexcitatory. Studies in rodents document orexin-stimulated elevations in blood pressure and heart rate (Chen *et al*., 2000; Monda *et al*., 2001; Samson *et al*., 1999; Shirasaka *et al*., 1999; Wang *et al*., 2001) and sympathetic outflow indicated by increased renal sympathetic nerve activity, plasma epinephrine, nor-adrenaline release, and firing rate of sympathetic nerves (Hirota *et al*., 2001; Matsumura *et al*., 2001; Monda *et al*., 2001, 2003, 2004; Shirasaka *et al*., 1999). Despite that peripheral orexin receptors have been identified intravenous orexin infusion failed to increase heart rate (Chen *et al*., 2000), which suggests that central sites of action such as the rostral ventrolateral medulla (Chen *et al*., 2000), nucleus of the solitary tract (de Oliveira and Ciriello, 2003; Smith *et al*., 2002), arcuate nucleus (Wang *et al*., 2003), hypothalamic paraventricular nucleus (Sato-Suzuki *et al*., 2002), and the diagonal band of Broca (Monda *et al*., 2004) may be largely responsible for the tachycardic response since OXA readily transverses the blood–brain barrier (Kastin and Akerstrom, 1999). However, interestingly, both heart rate and blood pressure are increased after infusion into the rostral ventrolateral medulla (Chen *et al*., 2000) and nucleus of the solitary tract (de Oliveira and Ciriello, 2003; Smith *et al*., 2002). In contrast, OXA has been shown to have negative effects as OXA in the nucleus ambiguous (de Oliveira and Ciriello, 2003) and the subfornical organ reduced heart rate (Smith *et al*., 2007), and OXA in the nucleus ambiguous (de Oliveira and Ciriello, 2003) had no effect on blood pressure but intra-subfornical organ OXA (Smith *et al*., 2007) reduced blood pressure. The significance of the brain site of infusion is underscored by comparing the pressor and tachycardic response to OXA across brain sites.

Orexins role in thermoregulation is exemplified by the stimulatory effect of OXA on the interscapular brown adipose tissue (iBAT), a thermosensitive organ rich in uncoupling protein one, which is largely responsible for adaptive thermogenesis in rodents. Despite that iBAT is lacking in adult humans, the relevance of brown adipose tissue to human thermogenesis has been hotly debated and recent studies suggest relevance to human obesity (Sellayah *et al*., 2011). Increased uncoupling protein one activity favors heat production rather than ATP production by shuttling protons across the inner mitochondrial membrane to dissipate the proton-motive force driving oxidative phosphorylation. Stimulation of sympathetic nerves innervating the iBAT stimulates colonic temperature, and cold exposure stimulates iBAT activity, which directly contrasts the effect of housing rodents above thermoneutral, which reduces iBAT activity. An early study demonstrated that OXA increased firing rate of sympathetic nerves innervating the iBAT (Monda *et al*., 2001) and iBAT temperature (Monda *et al*., 2001), both of which would be expected to increase thermogenesis and is consistent with OXA stimulation of colonic temperature (Monda *et al*., 2001, 2004; Wang *et al*., 2003; Zheng *et al*., 2005). Recently, Morrison and colleagues proposed a neuroanatomical basis for OXA modulation of thermoregulation through the rostral raphe pallidus and lateral parapyramidal area, which are sites of BAT sympathetic premotor neurons. Orexin A injection into the rostral raphe pallidus and lateral

parapyramidal area robustly increased iBAT sympathetic outflow, expired carbon dioxide and both core and iBAT temperature in anesthetized rats (Tupone *et al*., 2011). Although this suggests that OXA-modulation of temperature does in fact increase energy expenditure, heart rate was also increased. Contrary to the stimulatory effect of OXA on thermoregulation, OXA failed to increase temperature after chronic infusion (Haynes *et al*., 1999); however, it is plausible that the structural stability of OXA at body temperature may underlie this discrepancy. Thus, the cardiovascular, sympathetic, and thermoregulatory action of orexins support the stimulatory action of orexins on basal metabolism and total energy expenditure.

2. Physical activity—Physical activity contributes to energy expenditure and the promotion of physical activity by OXA is an irrefutable effect. Irrespective of the central site of microinfusion, OXA stimulates physical activity including locomotion, rearing, grooming, and burrowing behaviors after ventricular (Hagan *et al*., 1999; Ida *et al*., 1999) or intraparenchymal infusion. Further, a dose-dependent increase in physical activity is paralleled by elevated energy expenditure (Kiwaki *et al*., 2004). While the magnitude of OXA-induced physical activity varies with respect to the location of the microinjection (Kotz *et al*., 2008), the overall stimulatory effect remains consistent. Thus far, OXA infusion into the following brain sites has been shown to reliably stimulate physical activity: lateral hypothalamus, hypothalamic paraventricular nucleus, substantia nigra, tuberomammillary nucleus, dorsal raphe, nucleus accumbens, medial preoptic area, and locus coeruleus (Espana *et al*., 2001; Kiwaki *et al*., 2004; Kotz *et al*., 2002, 2006, 2008; Novak and Levine, 2009; Novak *et al*., 2006; Teske *et al*., 2006, 2010; Thorpe and Kotz, 2005). Likewise, OXA infused into the medial preoptic area and medial septum elicits grooming (Espana *et al*., 2001). Moreover, direct increases in muscle tone or EMG activity in specific muscles, which would be indicative of muscle tone, was observed following OXA microinfusion into the locus coeruleus (Kiyashchenko *et al*., 2001), the alpha gigantocellular reticular nucleus in the medioventral medullary region (Mileykovskiy *et al*., 2002), trigeminal motor nucleus, and hypoglossal motor nucleus (Peever *et al*., 2003). Interestingly, orexin into the pontine inhibitory area (Kiyashchenko *et al*., 2001) and the ventral gigantocellular reticular nucleus in the medioventral medullary region inhibited hindlimb muscle tone (Mileykovskiy *et al*., 2002). Despite that inhibition of hindlimb muscle tone would seem to contraindicate the increases in physical activity after OXA, parallel activation and suppression of muscles in opposition are required for movement, which would be essential for normal locomotion.

3. Sleep—The role of orexin in sleep/wake regulation and subsequent influence on energy expenditure is exemplified in the pathological sleep condition narcolepsy due to the loss of orexin-containing neurons or orexin receptors in humans and animal models (Chemelli *et al*., 1999; Lin *et al*., 1999; Nishino *et al*., 2000; Siegel, 1999). The symptomatology of narcolepsy, characterized by the inability to consolidate sleep or wake into long bouts, results in sleep fragmentation and sleep behavioral state instability (Mochizuki *et al*., 2004; Nishino *et al*., 2000; Sakurai, 2005; Willie *et al*., 2003). These symptoms are dampened by exogenous OXA in narcoleptic animals (Mieda *et al*., 2004), which highlights the importance of orexin in the maintenance and stabilization of sleep behavior.

Electrophysiological and molecular studies further support a role for orexin in the maintenance and stability of normal sleep and wakefulness. Orexin neurons display phasic firing patterns during wakefulness yet are silent during SWS (Lee *et al*., 2005; Mileykovskiy *et al*., 2005). In parallel, orexin levels display circadian rhythmicity and gradually increase in anticipation of the active phase and decrease prior to and during the rest phase (Fujiki *et al*., 2001; Lee *et al*., 2005; Yoshida *et al*., 2001). Not surprisingly, orexin levels also increase following sleep deprivation (Allard *et al*., 2007; Pedrazzoli *et al*., 2004; Wu *et al*., 2002). Orexin neuron activity during wakefulness is also modulated by the ascending arousal network including the sleep/wake regulating monoamines and acetylcholine (Li *et al*., 2002; Saper *et al*., 2010; Yamanaka *et al*., 2003) such that aminergic and cholinergic arousal circuits sustain orexin cells during wake (Estabrooke *et al*., 2001; Takahashi *et al*., 2008). These circuits in turn send inhibitory input to the ventrolateral preoptic area sleep-active neurons of the hypothalamus, and thereby further maintain wakefulness (Gallopin *et al*., 2000). Interestingly, orexin neurons also promote wake by actively hindering REM sleep by inhibiting the oral pontine reticular nucleus, a structure involved in the generation of REM sleep (Nunez *et al*., 2006). Thus, the absence of orexin results in reduced activity throughout the arousal network and culminates in an inappropriately low threshold for the transition into sleep from wake, which results in narcolepsy characterized by behavioral instability.

Orexins essential role in maintaining and stabilizing wake is consistent with previously mentioned actions of orexins, including the stimulation of total energy expenditure by promoting elevations in physical activity, body temperature, and sympathetic outflow. One of the earliest investigations on sleep found that between SWS and REM sleep, oxygen consumption was lowest during SWS and highest during REM sleep (Brebbia and Altshuler, 1965). Interestingly, studies in narcoleptic animals and humans suggest that narcolepsy-associated weight gain may be primarily due to reduced availability of orexin and behavioral instability, rather than hypersomnia (excessive active period sleep), as patients with idiopathic hypersomnia had a lower body weight (Kok *et al*., 2003). Like humans, mice lacking orexin weighed more than wild-type mice, yet they had reduced energy intake and physical activity (Hara *et al*., 2001). Thus, reduced metabolic rate and energy expenditure resulting from the absence of long wake bouts likely contributes to the increased body weight in orexin-deficient humans and animals. Furthermore, behavioral studies show that orexin antagonism increases sleep fragmentation (Beuckmann *et al*., 2004; Brisbare-Roch *et al*., 2007; Chen *et al*., 2006; Gerashchenko *et al*., 2001, 2003; Llewellyn-Smith *et al*., 2003; Thakkar *et al*., 1999) while central administration of OXA increases arousal and wakefulness and reduces both NREM and REM sleep (Bourgin *et al*., 2000; Espana *et al*., 2001; Hagan *et al*., 1999; John *et al*., 2000; Methippara *et al*., 2000; Piper *et al*., 2000; Rodgers *et al*., 2002; Xi *et al*., 2001), which is blunted by preinfusion with the OX1R antagonist SB 334867 (Smith *et al*., 2003). In a parallel manner, optogenetic silencing of orexin neurons induces SWS (Tsunematsu *et al*., 2011), while optogenetic activation of orexin neurons prompts mice to wake from sleep (Adamantidis *et al*., 2007; Carter *et al*., 2009). Thus, several studies highlight the importance of orexin in sleep/wake and observations from persons with narcolepsy and animals models of narcolepsy underscore its physiological significance.

Apart from the stimulating energy expenditure by promoting wake and activity, orexin modulates body temperature during sleep (Mochizuki *et al*., 2006). Orexin may have indirect effects on sleep and thermoregulation as OXA-induced physical activity during the day may increase body temperature and the accumulation of metabolic end products that promote sleep and heat loss in a circadian manner (Alam *et al*., 1996; McGinty and Szymusiak, 2001). At the neural level, orexin neurons reciprocally innervate the preoptic area, which promotes sleep and heat loss (Alam *et al*., 1995; Kumar, 2004) and thermal stimuli to the preoptic area strongly modulates sleep propensity and EEG delta activity (Kumar, 2004). Orexin terminals project to critical thermoregulatory brain sites including the tuberomammillary neurons, locus coeruleus, basal forebrain, pontine inhibitory area dorsomedial hypothalamus, ventromedial hypothalamus, posterior hypothalamus, periaqueductal gray, dorsal raphe nucleus, and intermediolateral column of the spinal cord (Kornum *et al*., 2011; Mochizuki *et al*., 2006). Thus, orexins are neuroanatomically positioned to modulate thermoregulation and contribute to heat loss during sleep (Ohno and Sakurai, 2008).

Overall heat loss, due to reduced production and increased loss, is an essential aspect of sleep (Mochizuki *et al*., 2006), which underscores the energy conservation function proposed for sleep. Circadian modulation of body temperature may also alter sleep propensity (Kumar, 2004), which would be expected to have energetic consequences. In parallel, a moderate fall in body temperature may be necessary for good-quality sleep (Gilbert *et al*., 2004). When compared to persons with normal sleep quality, the normal decline in body temperature is blunted in individuals with poor sleep quality (Lushington *et al*., 2000; Pierangeli *et al*., 2001; Zepelin and McDonald, 1987). Thus, it is feasible that altered thermoregulation also contributes to sleep fragmentation in narcolepsy (Mochizuki *et al*., 2006). Indeed, Mochizuki *et al*. showed parallel 24 h rhythms of physical activity, wake and body temperature in wild-type mice (Mochizuki *et al*., 2006). This demonstrates an association between vigilance states and energy expenditure, which was less prominent in orexin knockout mice. Importantly, while both wild-type and orexin knockout mice exhibited declines in body temperature during sleep, temperature declined to a lesser extent during sleep in orexin knockout mice. Likewise, elevations in body temperature during active wake were minor in orexin knockout mice compared the elevations in wild-type mice. Hence, the blunted decline in body temperature may be due to the intermittent awakenings during sleep (Mochizuki *et al*., 2006) while the dampened increase in body temperature may be due to shorter wake bouts and physical activity during wake in the orexin knockout mice (Mochizuki *et al*., 2004). In sum, these data reiterate a role for orexin in heat loss during sleep, possibly through sleep stabilization (Mochizuki *et al*., 2006).

It is plausible that orexin effects on sleep/wake are also modulated by the autonomic nervous system. During wake, orexin inhibits the heat loss-inducing parasympathetic nervous system (Dergacheva *et al*., 2005) and promotes sympathetic nervous system activity. In contrast, during sleep, orexin neuron activity and orexin levels are low while parasympathetic activity predominates (Kuo *et al*., 2008). As noted above, exogenous orexin activates the sympathetic nervous system and orexin injection into the raphe pallidus increases sympathetic outflow to the brown adipose tissue, which increases thermogenesis

(Morrison and Nakamura, 2011; Tupone *et al*., 2011). Conversely, mice lacking orexin have impaired brown adipose tissue thermogenesis (Sellayah *et al*., 2011; Vijgen *et al*., 2011). Thus, these data imply that orexin potently enhances energy expenditure, via stimulation of sympathetic activation and suppression of parasympathetic activity.

II. Conclusion

Orexins provide a crucial link between energy balance and arousal. The orexin neurons functionally interact with neural pathways for physical activity pathways and sleep and cardiovascular and temperature regulatory centers in the brain, which positions orexin neurons to coordinate energy expenditure and the sleep–wake cycle. Corollary to this, obesity in humans and animal models is associated with altered sleep, reduced physical activity, and plasma and hypothalamic levels of orexin, whereas weight loss is associated with increased orexin levels in the plasma and improved sleep quality. These studies suggest that reduced component-specific energy expenditure due to lack of physical activity may culminate in weight gain in narcoleptic and obese humans as well as in orexin-deficient animals. Thus, the orexin system may act as a sensor for metabolism and send signals to intra- and extrahypothalamic targets to modify behavioral outputs based on energy needs.

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