Motivational activation: a unifying hypothesis of orexin/hypocretin function

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Abstract

Orexins (hypocretins) are two peptides (orexin A and B) produced from the pre-pro-orexin precursor and expressed in a limited region of dorsolateral hypothalamus. Orexins were originally thought to specifically mediate feeding and promote wakefulness, but it is now clear that they participate in a wide range of behavioral and physiological processes under select circumstances. Orexins primarily mediate behavior under situations of high motivational relevance, such as during physiological need states, exposure to threats or reward opportunities. We hypothesize that many behavioral functions of orexins (including regulation of sleep/wake cycling) reflect a fundamentally integrated function for orexins in translating motivational activation into organized suites of psychological and physiological processes supporting adaptive behaviors. We also discuss how numerous forms of neural heterogeneity modulate this function, allowing orexin neurons to organize diverse, adaptive responses in a variety of motivationally relevant situations. Thus, the involvement of orexins in diverse behaviors may reflect a common underlying function for this peptide system.

The essence of the beautiful is unity in variety. —Moses Mendelssohn

Since their simultaneous discovery by two groups[1,2], orexin/hypocretin neurons have been implicated in numerous functions, including regulating sleep/wake cycles, arousal, reward seeking, cognition, motor activity and stress responses, and influencing cardiovascular, respiratory, metabolic and homeostatic functions. Such functional diversity is not uncommon in the hypothalamus, which is well known for integrating neural and hormonal signals to promote survival-related behaviors. Orexin neurons also project throughout the CNS, suggesting a potentially widespread influence of this restricted neuronal population.

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What does this apparent diversity of function signify about the roles for orexin neurons in behavior?

Here, we first briefly summarize the major known functions of orexins (based on animal studies and orexin-deficient human populations) and argue that the orexins' role in each involves 'motivational activation'. That is, motivation (the psychological drive underlying goal-directed behavior) is facilitated by orexins during specific environmental challenges or opportunities. Orexin-facilitated motivation is recruited by homeostatic signals of physiological disequilibrium and/or exposure to important environmental stimuli, especially when they are relevant to a current physiological need. We propose that orexins help to transform motivational activation into adaptive behavior directed toward managing/ exploiting the challenge/opportunity at hand. They do so by facilitating suites of psychological processes (for example, appetitive or aversive motivation) and physiological processes (for example, cardiovascular activation, suppression of sleep, etc.), all facilitating adaptive behaviors—a variety of responses in service of this unified underlying function. We also suggest that disruption of this integrated orexin function substantially contributes to sleep/wake disturbances seen in narcolepsy/cataplexy (NC). Finally, we discuss how heterogeneity and plasticity among orexin neurons, their afferents, and orexin and co-transmitter signaling in efferent target structures modulate this integrative role for orexins, facilitating appropriate behaviors in many different situations.

The many faces of orexin/hypocretin function

Arousal and sleep/wake transitions

Perhaps the best-known function of orexins is in promoting arousal and waking from sleep. Orexin administration lengthens, and orexin disruption shortens, continuous periods of wakefulness[3–5], and loss of orexin neurons or receptors are associated with NC in rodents, dogs and humans[4,6–8]. Orexin projections excite wake-promoting systems, including locus coeruleus (LC) norepinephrine, dorsal raphe serotonin, tuberomammillary histamine and basal forebrain (BF)/brainstem acetylcholine neurons[4,5,9–11]. Orexin neurons are more active during wake than sleep, frequently fire just before waking and cause waking within several seconds when optogenetically stimulated[3,7,12,13].

However, rather than acting simply as an arousal on/off switch, the orexin system's role in wakefulness may be more akin to that of its ascending modulatory system targets (for example, dopamine, norepinephrine). Similar to orexin neurons, these systems are active during wakefulness, and stimulating them induces waking from sleep, but this does not imply that they primarily function to cause arousal[14,15]. Indeed, loss of orexin function does not result in loss of waking, nor does it cause changes in the total daily time spent in sleep versus wake[6,16]. Instead, humans and animals with NC exhibit unusual intrusions of sleep in the active period and wake in the rest period[5,6,16,17].

We propose that this results from a role for orexins in motivational activation, superimposed on a circadian oscillation in orexin neuron excitability. The orexin system exhibits two arousal-related patterns of activity: long-term circadian oscillations in orexin release/ cerebrospinal fluid levels and phasic, behavior-related bursts of orexin neuron firing. Orexin

circadian rhythmicity is controlled closely (though likely indirectly) by the suprachiasmatic nucleus (SCN), which causes basal excitation of orexin neurons during the active period[6,11]. Orexin neuron firing also varies substantially throughout wakefulness, with both tonic activity[13,18] and rapid firing specifically during periods of adaptive behavior, such as exploration, play, predation and grooming, but not during other behaviors matched for physiological arousal and locomotor activity[12,19,20]. This is consistent with the role we propose for orexins in the motivational processes underlying these adaptive behaviors (associated with phasic firing), which is overlaid on circadian oscillations in tonic activity, excitability or peptide release (Fig. 1).

These roles for orexins in motivated behaviors and in arousal are mutually supportive, as adaptive, motivated behavior necessarily requires wakefulness. We propose that SCN-dependent tonic excitation during the active period not only increases orexin baseline firing and release[6,11], but also increases the ability of other excitatory inputs to activate orexin neurons[21], potentiating phasic firing during adaptive behaviors *in vivo*[12]. Thus, we hypothesize that both SCN-dependent tonic excitation and phasic orexin neuron burst firing help to produce and maintain wakefulness—the latter as a consequence of increased motivation to engage adaptive challenges or opportunities. This is consistent with the view that orexins prolong arousal in the service of managing environmental threats or opportunities[4,10,19,22–24].

The orexin system's ability to promote wakefulness is opposed by a homeostatic sleep pressure signal that accumulates in a linear fashion with wakefulness duration. Such sleep pressure increases until the onset of sleep, and subsides during sleep until reaching a nadir, when waking can occur[25]. Notably, orexins compete with sleep pressure to control activity in sleep- and wake-generating brain circuits[6,11,26]. For example, optogenetic orexin neuron stimulation that normally produces waking fails to do so after induction of sleep pressure via sleep deprivation[7] (although rebound sleep after deprivation is fragmented in orexin knockout mice, despite accumulated sleep pressure[16]).

In NC humans or animals, an inability of circadian or motivation-related orexin activity to oppose homeostatic sleep pressure and maintain wakefulness can explain the deconsolidation of both waking and sleep seen in the disorder, in accordance with the two-process model of sleep-wake regulation[25] (Fig. 1). This hypothesis explains dysregulated sleep/wake cycling associated with orexin neuron loss in NC, but does not explain cataplexy symptoms. How cataplexy relates to motivational or arousal functions of the orexin system is controversial, but a link to emotional arousal is clear[7,11,19,23,27–29] (Box 1).

In sum, we propose that, although orexins are closely associated with arousal and wakefulness, they are neither necessary nor sufficient for either. Instead, orexins promote arousal/wakefulness as a component of their role in motivational activation.

Reward seeking

Food intake functions were proposed by researchers that initially described orexins/hypocretins because orexin administration produces feeding, and food deprivation increases orexin mRNA[1,2]. This hypothesis is also consistent with the fact that this region of

hypothalamus is well known to mediate feeding and other appetitive behaviors[1,30,31]. Subsequent studies demonstrated that orexin neurons are excited by peripheral signals of nutrient need (for example, ghrelin), inhibited by satiety signals (for example, glucose), and interact with feeding peptides to promote food consumption and seeking[4,32–35].

However, recent evidence has clarified that the orexin system is not indiscriminately linked to feeding, but instead mediates seeking and consumption of palatable foods, food seeking that is highly motivated by hunger, or seeking that is elicited by Pavlovian cues[30,32,34,36]. Notably, orexin neurons are active during hunger and help to translate peripheral hunger signals into increased appetitive responding for food and food cues[32,34,37,38]. Thus, orexins facilitate food seeking and feeding especially in motivationally charged circumstances.

Orexins have a parallel role in motivation for addictive drugs. Our laboratory first demonstrated that orexin neurons respond to drug cues and mediate drug seeking via projections to the ventral tegmental area (VTA)[30,31,39,40]. Numerous reports have since shown that seeking for all major addictive drugs involves orexin neurons[36]. Reminiscent of their role in food seeking, orexins are preferentially involved in highly motivated drug seeking (for example, under progressive ratio reinforcement schedules or seeking that is triggered by salient external stimuli such as drug-paired cues or stressors)[30,36,39,41–43]. Acute drug withdrawal also involves orexins, leading some to speculate that orexin neuron activity during withdrawal facilitates drug seeking to alleviate this specific 'drug need state'[42]. In sum, orexins have a crucial, but conditional, role in facilitating reward seeking, primarily when the external world and/or the internal milieu signals a need for highly motivated action.

Stress

Orexins orchestrate various aspects of stress responses, including arousal, attention, anxiety- or panic-like states, and grooming, as well as hypothalamic-pituitary-adrenal axis, cardiovascular and respiratory activation[10,44–46]. Orexins interact with classical brain stress systems (for example, corticotropin releasing factor (CRF), norepinephrine, extended amygdala)[5,7,10] and reside in a part of the hypothalamus associated with fight or flight responses[46]. They are also required for stress-related aspects of addiction[42].

Although the orexin system can promote stress responses, its role is neither exclusive to stress (for example, orexin signaling facilitates non–stress-related reward seeking) nor common to all types of stress. Only behavioral/physiological responses to certain acute stressors are mediated by orexin in rodents, including foot shocks, shock-associated or novel contexts, short-term forced swimming or restraint, food restriction, panic-like states, and social stress[31,41,45–47]. These stressors all elicit adaptive coping responses, such as escape attempts, conspecific aggression/submission, novelty exploration or freezing in a shock-associated context.

In contrast, chronic, inescapable stressors (such as the types used in animal models of depression) generally yield both cessation of coping responses and downregulation of orexin transmission. For example, acute (but not chronic and predictable) stress is associated with orexin neuron activation[41] and chronic stress can disrupt orexin signaling in target regions[48].

In humans (including NC patients), depression symptoms have been associated with orexin system hypoactivity in some (but not all) studies[17,41,46,49]. Conversely, increased orexin function is associated with antidepressant effects in chronically stressed animals[50].

Thus, increased signaling by orexins may help to organize stress responses, but only when motivated, adaptive coping behaviors are undertaken during potentially escapable stressors. In contrast, when a stressor is chronic, predictable and impossible to escape, orexin system hypoactivity could yield depression-like, amotivational symptoms[41,46,51].

Homeostatic regulation

Orexin neurons respond not just to homeostatic feeding signals, but also to signals of several physiological need states. For example, orexin neurons depolarize when blood CO_2 levels rise, causing increased respiration via brainstem projections[33,44]. As with other orexin-dependent behaviors, homeostatic modulation of breathing is conditional, occurring predominantly when animals are awake and active[44]. Intriguingly, application of CO_2 to orexin cells reduces their responsiveness to glucose, meaning that at least some orexin cells respond to multiple homeostatic signals, potentially to help prioritize different behavioral strategies (breathing/feeding) on the basis of need hierarchies[33].

Orexins have a similar conditional role in other peripheral physiological functions. For example, the orexin system activates cardiopulmonary responses specifically during motivational activation, and orexins increase peripheral thermogenesis specifically when animals are cold[44,52]. This sensitivity of orexin neurons to multiple specific needs implies a common role in promoting homeostasis by sensing physiological needs and promoting corresponding adaptive responses to address them.

Cognition: attention, learning and memory

Orexin neurons facilitate cognition, especially attention and certain types of learning[53]. This is achieved via direct projections to medial prefrontal cortex (mPFC), where orexins increase sustained attention[54], and modulation of BF neurons, facilitating attention by causing mPFC acetylcholine release[9]. However, systemic orexin 1 receptor blockade does not affect attention, instead reducing impulsivity, in a five-choice reaction time task[55], consistent with a role for orexins in facilitating appetitive motivation.

Orexins may also have a role in aversive and appetitive learning, although evidence for this is limited and somewhat mixed. Acquisition of Pavlovian fear conditioning involves orexinergic projections to LC[56], and orexin neurons are activated via CRF during an unconditioned shock stimulus[47]. Hippocampal orexins are also required for learning and performance in a Morris water maze task, which involves using spatial memory to escape from forced swimming[57]. Orexin neurons are required for attentional aspects of motivated learning[53], and acquisition of morphine conditioned place preference activates and requires LH orexinergic projections to VTA[31] (although orexin 1 receptors are not required for Pavlovian cue/cocaine learning in a self-administration/reinstatement procedure[58]).

Orexins facilitate attention and some types of learning, but little more is known about their roles in cognition, learning and memory. On the basis of orexin functions in several

processes described above, we predict that orexins primarily promote learning and cognition that involves emotionally or motivationally relevant stimuli (for example, fear or place preference conditioning), but not non-emotional/motivational forms of learning (for example, stimulus-response habits or habituation learning).

A unified underlying function for orexin neurons?

We have summarized some of the primary behavioral and physiological processes in which orexins participate and note that orexins' roles are conditional for each process. Orexin neurons are involved in arousal, sleep/wake, homeostatic and metabolic regulation, but these functions vary according to motivational state, sleep pressure, circadian rhythms and other variables. Orexins facilitate reward seeking, but only when this seeking is highly motivated by a physiological need, such as hunger, and/or by a psychological need triggered by substantial external stimuli, such as cues or stressors. Orexins help coordinate stress responses, but only for certain acute stressors in which escape or other coping strategies occur, and not when stress is chronic, predictable and inescapable. Orexins can also facilitate attention, but are only involved in certain types of emotional learning.

We propose that a common theme underlying these diverse processes is recruitment of the orexin system during motivational activation triggered by internal (homeostatic) or external (motivationally relevant) signals of threat or opportunity. We also propose that orexins fundamentally function to facilitate adaptive, often highly motivated behavior by coordinating psychological and physiological responses supporting such behaviors to address the threat or opportunity at hand. However, if orexins function in this integrated manner, heterogeneity at some level must modulate the orexin system to allow coordination of diverse, contextually appropriate behaviors, adding flexibility and variety to orexins' unified function.

Sources of variety in the orexin system

Heterogeneity in the orexin system depends on at least three factors: diversity of the cells themselves, diversity in their inputs and/or diversity in efferent target responses to orexin neuron activity.

Heterogeneity amongst orexin neurons

Several groups have documented heterogeneity in orexin neuron function based on anatomical position in the mediolateral axis of the orexin field. Orexin neurons medial and dorsal to the fornix (dorsomedial and perifornical hypothalamus) express Fos in relation to wakefulness and aversive stimuli, whereas those lateral to fornix (lateral hypothalamus) are instead activated during conditioned food or drug reward seeking[3,31,59], although some studies have not found a clear aversion/reward dichotomy[10]. Topographical differences could reflect differential connectivity of medial versus lateral orexin cells with wider avoidance- versus approach-related circuits. However, although some connectional specificity has been reported[9,60], these differences are frequently subtle[10].

Orexin neuron heterogeneity may also result from differential or plastic orexin peptide expression and/or trafficking of orexin A and B, which have different affinities for the two orexin receptors[2]. In addition, orexin peptide expression is up- or downregulated by many factors, including motivational or physiological state and prior stress or reward exposure, perhaps reflecting epigenetic or transcription factor–based modifications of orexin production[50,61]. This dynamic modulation of orexin expression implies that the mere identity of a neuron as orexinergic or non-orexinergic could be mutable.

The term orexin neuron also obscures the fact that these neurons coexpress other transmitters that can modulate the synaptic and behavioral effects of orexins. For example, virtually all orexin neurons coexpress the opioid peptide dynorphin[55,62]. Orexins and dynorphin can be packaged in the same synaptic vesicles and can have directly opposing electrophysiological and behavioral actions (at least in VTA[55]). However, orexin and kappa opioid receptors are heterogeneously distributed among synaptic compartments and cell types across target regions, yielding substantial heterogeneity in orexin/dynorphin effects[33,63]. Because most prior experiments have disrupted orexin signaling (for example, with antagonists or receptor/peptide knockout) while sparing dynorphin and other signaling, there is still much to learn about orexin/co-transmitter interactions.

The majority of orexin neurons also contain glutamate, which can signal independently from orexin[64]. As with other neuropeptides, orexin neurons may signal predominantly with classical transmitters when firing slowly, and peptides such as orexins and dynorphin when firing in a rapid bursting pattern[64]. This could imply functionally distinct slow- and fast-firing modes for orexin neurons, as previously proposed[7].

In addition, at least two subpopulations of orexin neurons (termed H and D neurons) exist[33]. These subtypes vary in their anatomical and electrophysiological characteristics, but not in their likelihood of projecting to LC or VTA or their expression across the mediolateral extent of the orexin field. This newly discovered diversity is intriguing, but its functional consequences are not yet clear.

Heterogeneity in orexin inputs

Several factors can influence how and when orexin neurons are recruited during behavior. First, orexin neuron afferents may selectively target subsets of orexin neurons, potentially allowing for differential recruitment of functional subpopulations of orexin neurons[59,60]. Signals of diverse physiological and psychological needs also regulate orexin neuron activity, and some orexin neurons respond to multiple such signals (for example, CO_2 and glucose[33]). However, heterogeneity in receptor expression also exists. For example, ~60% of orexin neurons express CRF receptors, about 25% respond to CRF *in vitro*[47] and glucose responses are similarly variable[33,35]. In addition, motivationally important experiences such as cocaine exposure, food restriction or sleep deprivation elicit plasticity in excitatory inputs to orexin neurons, indicating that stimuli capable of recruiting orexin neurons change on the basis of learning and motivational state[41,65]. However, there remains much to be learned about the contribution of input heterogeneity and plasticity in orexin functions (Box 2).

Heterogeneous processing in efferent targets

Orexin function is modulated at the level of efferent targets in several different ways. First, not all orexin neurons project to all regions known to receive orexinergic input. Individual orexin axons are collateralized and frequently target several adjacent structures, but few neurons project both to BF and LC (for example, see ref. 10). This implies that orexins participate in multiple parallel, but anatomically segregated neural circuits. The principles governing this heterogeneity are still largely unknown[10,33].

Orexin receptor distribution also determines orexins' effects in efferent target regions. Orexin peptides act at OX1 and OX2 receptors, which have broad and partially non-overlapping distributions, allowing for target-specific effects of orexin release[4]. Both receptors can also be expressed pre- or postsynaptically, and although they usually couple to G_q proteins, they can also engage G_s, or G_i pathways[33,63]. In addition, synaptic and behavioral effects of orexins can be dynamic; for example, orexins can inhibit target neurons via preand postsynaptic mechanisms during day and night, respectively[66]. Numerous studies have suggested that stimulation of OX1 and OX2 receptors, independently or together, produces different functional results[3,4,7,10,36,63]. In general, sleep/wake regulation is most closely tied to OX2 receptors, whereas reward-related behaviors are more closely associated with OX1 receptor activation[36].

Finally, interaction of orexins with other synaptic activity in target regions also crucially modulates its synaptic and behavioral effects. For example, orexins facilitate glutamatergic transmission via longterm potentiation–like processes in VTA dopamine neurons, and this interaction is required for reinstatement of cocaine seeking[22,30,36]. We hypothesize that orexins increase the gain of motivation-related glutamatergic inputs to dopamine cells (from mPFC or other sources), facilitating conditioned reward seeking[36,40]. This neuromodulatory role may be a common principle of orexin signaling[36,64,67].

In sum, orexin signaling is complex and heterogeneous and is subject to input and output plasticity modulated by circadian and experiential factors. We propose that such heterogeneity refines the orexin system's underlying function in motivation, facilitating specific behaviors and physiological processes appropriate for the threat or opportunity at hand.

Integration among multiple orexin functions: unity in variety

Here, we propose that orexins have a fundamentally unified role that spans a variety of processes, including arousal, reward seeking, homeostatic regulation and stress, which we term motivational activation. This underlying function facilitates appetitive or aversive motivation and related physiological responses in service of producing behaviors to address pressing threats or opportunities.

However, if orexins have an integrative role as we have proposed, this must be embedded in heterogeneous functional connectivity with wider circuits for orexins to generate diverse behaviors. Heterogeneity in orexin cell subpopulations and their inputs, as well as synaptic consequences of orexin transmission in efferent targets, may therefore result in parallel

information streams, each involving orexins in a qualitatively similar manner, but differentially interacting with separate wider circuits (for example, of approach versus avoidance). A tremendous amount has been learned about the functions and properties of orexin neurons since their discovery 16 years ago, and rapid development of neuroscience tools[7,12,23,48,50,66,68] gives hope for answering many remaining questions about this deceptively complex peptide (Box 2).

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Box 1

What can NC tell us about orexin function?

Key observations

- Cataplexy involves brief episodes of muscle atonia (paralysis) with maintained consciousness, often triggered by strong positive emotional stimuli in humans and animals[3,6,8,11,28,29].

- Orexin cerebrospinal fluid levels in NC are very low or absent, but this is not necessarily the case in narcolepsy without cataplexy[6,17].

- NC-like symptoms occur with orexin disruption in humans, dogs and rodents. Both OX1 and OX2 receptors, as well as co-transmitters lost with orexin cells, may be involved in NC[4,8,68].

- Mounting evidence indicates that an autoimmune response causes orexin neuron loss in human NC[69].

- NC patients show abnormal emotional processing and decision-making, likely involving amygdala[17,70–72], and orexin is released in human amygdala during positive emotions[73]. mPFC and amygdala are required for emotional stimuli to induce cataplexy in orexin knockout mice[28,29].

- NC patients are often prescribed stimulant or sedative drugs for sleep disturbances and may be less likely to abuse these drugs[4], although additional testing of this hypothesis is needed[17].

- Muscle atonia in cataplexy shares similarities to atonia in REM sleep, including a common effector circuit involving the medulla and sublaterodorsal nucleus projections to spinal motor neurons[11]. This indicates that cataplexy may involve inappropriate intrusion of REM sleep features (atonia, hypnogogic hallucinations) into the waking period[11]. However, it is unclear why emotional activation in particular would trigger intrusions of REM-like features[27].

Hypothesis: cataplexy as a feature of orexins' role in motivational activation

- Cataplexy may result from poor coordination of adaptive behaviors during motivational/emotional activation.

- To facilitate appropriate responses during threats or opportunities, orexins promote adaptive behaviors and inhibit competing behaviors. Corresponding to this, orexins facilitate top-down control of muscle activity and suppress competing networks, including the medullary-spinal atonia circuit[27,74].

- In NC and animal models of orexin dysfunction, emotional/motivational activation fails to engage orexin signaling, and atonia circuits are not adaptively inhibited, yielding episodes of cataplexy.

Box 2

Outstanding questions about integration and heterogeneity in the orexin system

- Do subpopulations of orexin cells mediate different aspects of its integrative function in motivational activation?

- If so, do these subpopulations differentially connect with wider circuits? Does this functional connectivity relate to medial versus lateral, or other orexin neuron subpopulations?[33,59]

- Orexin neurons show variability and plasticity in their afferent inputs, expression of orexin peptides (A versus B), co-transmitters, receptors and other factors. How is this heterogeneity regulated and how does it relate to other known sources of orexin heterogeneity, such as anatomical connectivity patterns?

- How do orexins and their co-transmitters interact and regulate target structure synaptic signaling? Do such interactions vary by target structure and/or is it based on dynamic changes in transmitter production, trafficking and release?

- Dynorphin is coexpressed in nearly all orexin neurons and can have opposite effects on synaptic signaling and behavior[55,62]. Is this 'push-pull' feature a fundamental property of orexin signaling? Are orexin/dynorphin peptides or transmitters dynamically regulated to favor predominant signaling by orexins/ dynorphin? If so, what are the factors that influence this regulation?

- How does orexin neuron firing rate affect orexin function? Do these neurons show clear tonic and phasic firing modes, perhaps related to circadian influences and motivated behaviors, respectively? Do subpopulations of orexin neurons differ in their firing properties?

- What is the connection between dysregulated sleep/wake transitioning and cataplexy in narcolepsy with cataplexy? Do these effects of disrupting orexin signaling reflect separate roles for orexin in basal sleep/wake regulation and atonia suppression during emotional activation, or do both result from loss of a common underlying orexin function?
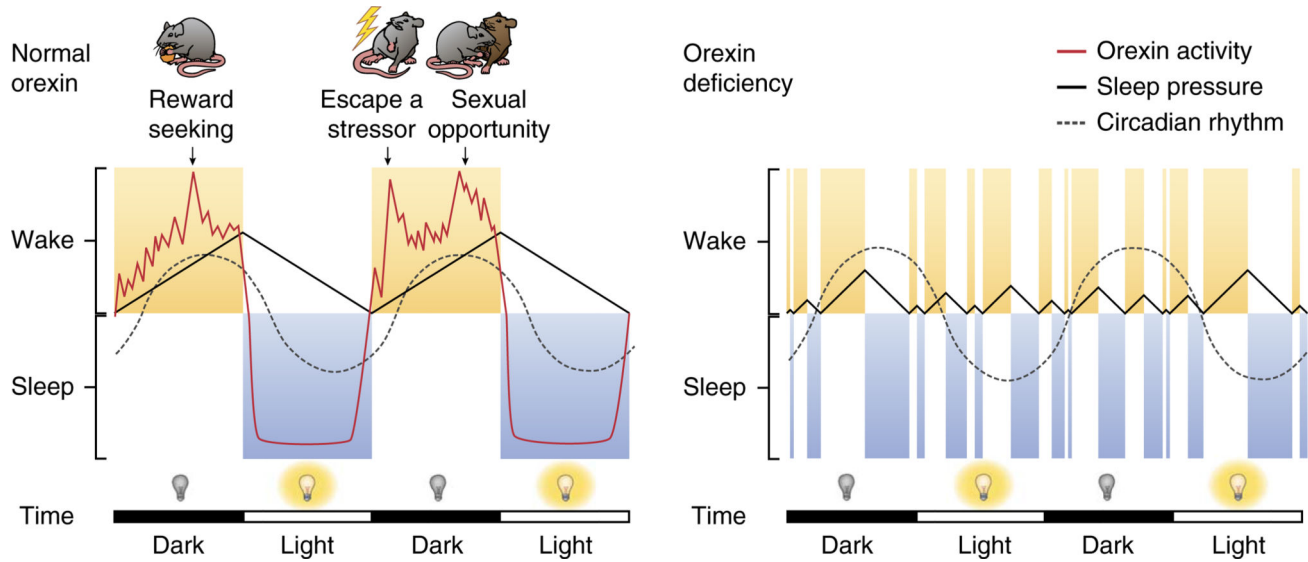
Figure 1.
Model of orexins' functions in sleep/wake regulation. Left, sleep/wake activity is homeostatically controlled, with sleep pressure (black solid line) increasing as a function of time awake and subsiding gradually over time asleep until sufficiently reduced to allow waking. Conversely, wakefulness is driven by a circadian signal (dashed gray line) that activates orexins and other arousal systems[3,4,6,10,25]. Orexin neuron activity (red line) has a circadian pattern, but also phasic bursts during waking as a function of motivational state and adaptive behavior. Orexins excite wake-active (for example, LC and dorsal raphe) and inhibit sleep-active brain regions (for example, medullary REM muscle atonia circuit), so discharge of orexin neurons during wakefulness helps to counteract sleep pressure and decrease the probability of sleep initiation, especially during emotionally arousing situations[4,11,19]. For purposes of clarity, sleep and wake periods have been depicted as uninterrupted, although rodents typically display multiple sleep/wake transitions in both light and dark phases. Right, in orexin-deficient subjects (for example, NC humans, or animal models of NC), even relatively low levels of unopposed sleep pressure can result in inappropriate intrusions of sleep, regardless of circadian phase or motivational state. Conversely, lower peaks of homeostatic sleep pressure (resulting from decreased wake epoch durations) result in shorter periods of recovery sleep to regain homeostasis, allowing inappropriate intrusion of waking in the rest phase. This mechanism might account for rapid sleep/wake transitions seen in narcoleptics and orexin-deficient animals.