Orexin Signaling System—Potential therapeutic Targets for Alzheimer's Disease and Various Mental Diseases

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Abstract

Background: Orexin (Orexin), also known as hypothalamic secretin (Hypocretin), is an important central neuropeptide involved in many physiological processes in the body, such as the regulation of diet behaviour, sleep-wake cycles and learning and memory functions. In the nervous system, orexin defects can cause narcolepsy. Other studies have shown that orexin is involved in emotional changes, reward behaviour, adaptation, stress, stress response and a series of body behaviour responses.

Objective: To summarize the physiological function of orexin. This study provides new ideas for the diagnosis and treatment of Alzheimer's disease and other diseases.

Conclusion: Orexin can not only treat sleep-wake disorders in Alzheimer's disease but also in narcolepsy, depression and addiction.

Keywords: Orexin • Insomnia • Narcolepsy • Depression • Addiction

Introduction

Since its discovery in 1998, the hypocretin/orexin system has been known to play multiple roles in the human body, including the regulation of sleep-wake cycles, feeding, reward and addiction, body temperature, and various other systems [1,2]. A more accurate understanding of the orexin signaling system is needed to develop more effective treatments. This paper summarizes the role of the orexin signaling system in several diseases, including Alzheimer's disease, narcolepsy, and addiction. The potential clinical applications of the Orexin Dual Receptor Antagonist (DORA) are also discussed. Orexins are produced by a very limited number of nerve cells, with approximately 3,000 nerve cells in rodents and up to 70,000 nerve cells in humans being capable of their production. OX1R is mainly expressed in cerebral cortical areas and brain stem nucleus sites, and it is involved in the regulation of sleep, arousal and addiction [3, 4]. OX2R is expressed primarily in histaminergic neurons in the nodule papillary nucleus and serotonergic neurons in the brain stem, nucleus accumbens, and striatum; its main function is to promote arousal. The histaminergic neurons originate from the lateral hypothalamus and project widely throughout the CNS [5]. The widespread projection of orexin-producing neurons and the involvement of the orexin system in regulating arousal, foraging, addiction, mood regulation, cardiovascular, and neuroendocrine systems are closely related [6]. With further study of orexin signaling systems, it is reasonable to believe that more effective treatment options will be developed in the future [7, 8]. Furthermore, a better understanding of the orexin signaling systems should contribute to new ideas and methods to treat diseases.

Literature Review

Dora and insomnia

Insomnia hazard: Primary insomnia is a disorder characterized by several symptoms, including difficulty falling asleep, waking up many times every night, waking too early and poor sleep quality.

An estimated 33% to 50% of adult's experience insomnia, and 9% to 12% of adults have chronic insomnia; the incidence in elderly patients has been reported to be as high as 20% [9]. Insomnia refers to the inability to sleep and/or frequently waking during sleep, and a lack of undisturbed sleep may cause symptoms such as daytime fatigue, daytime sleepiness, memory or inattention, anxiety, depression, irritability, reduced energy, and lack of motivation [10]. In turn, insomnia may affect mood, work performance, relationships, and daily functioning. The orexin dual-receptor antagonist, a class of drugs that can aid in resolving both sleep and sleep maintenance problems, does not damage postural stability and cognitive ability in the morning [3]. Dual-orexin receptor antagonists are expected to be an important new treatment option for insomnia patients.

Possible mechanism of Dora affecting sleep: Orexin Dual Receptor Antagonists (DORAs) were developed by Merck as a drug for the treatment of insomnia. The drug was approved by the FDA in 2014 and is mainly used to treat difficulties falling asleep and/or maintaining sleep in patients with insomnia. The DORA selectively blocks the orexin-mediated awakening system to promote sleep by realizing the transition to sleep. This is especially important in maintaining a long, consolidated period of rest [11]. Orexin neurons connect the ventral optic area (promotes sleep) and the brain stem (promotes wakefulness) to reduce antagonistic cortical excessive excitation. By activating regions of the brain that promote wakefulness to stabilize behaviour, orexin prevents unnecessary conversion between sleep and wakeful states. In chronic insomnia patients, low plasma orexin-A levels cause patients to have difficulty falling asleep and excessive awakening. In these patients, orexin neurons discharge when the patients are awake and stop firing during their sleep; therefore, blocking orexin signalling can theoretically reduce insomnia symptoms [12]. In animal studies, the efficacy of orexin antagonists has been demonstrated in dogs awakened during treatment with Almorexant (ACT 078573, an effective orexin receptor Orexin 1 receptor (OX1)/ Orexin 2 receptor (OX2) antagonist) [13].

Efficacy and safety of Dora: A study found that suvorexant (Belsomra, an orexin receptor antagonist and the first approved drug of this class) can improve sleep onset and maintenance after overnight treatment for more than three months and is generally safe and well tolerated [14]. It does not appear to significantly alter the underlying sleep structure characteristics compared to placebo. The most common adverse events associated with suvorexant are mainly the expansion of pharmacological activity, namely, lethargy, fatigue and dry mouth [15]. When drowsiness occurs, its severity is generally mild to moderate and rarely requires treatment interruption. The risks of narcolepsy and other associated adverse reactions appear to be dose related, with more adverse reactions reported at higher doses than at lower doses. Other adverse reactions have included signs of muscle weakness, strange dreams, sleepwalking, abnormal thoughts and behaviours [16]. Although drowsiness can be prominent and some normal attention processes may be affected, it is not necessary for patients to stop driving when taking this medication [17]. Patients with an inconsistent circadian system and ideal sleep/wake times with a short daytime sleep duration and poor quality may also benefit from orexin antagonists [18]. Elevated orexin may lead to sleep disruption, and DORA is well tolerated, with a demonstrated ability to promote sleep initiation and maintenance in

insomnia patients to achieve continuous improvement in sleep time. Orexin plays a key role in controlling arousal and sleep/wake switching [19].

Dora and cognition

Orexin neuropeptides play a strong arousal-promoting function in sleep-wake behaviour, and orexin neurons are present in many brain areas that are important for cognition, executive function, learning and memory. Several studies have shown that DORAs can stimulate neurogenesis in the dentate gyrus of the hippocampus, which regulates learning and memory [19]. These data suggest that the orexin/hypothalamoprotein system is a good potential therapeutic target and an important mechanism in the regulation of cognitive function [20, 21]. Promoting sleep by reducing orexin signaling may reduce the risk of cognitive and motor impairment compared with GABAergic drugs [22].

Sleep makes memory more profound: Sleep facilitates the reactivation and consolidation of newly acquired memories. The human brain selects noteworthy information for reprocessing during sleep. REM (Rapid Eye Movement Sleep) and SWS (Slow Wave Sleep) are believed to have important roles in memory processing based on modern memory research conducted both in animal and clinical experiments. Sleep, in addition to strengthening established memories, can support the conversion of memories between the hippocampus and neocortex, integrating memory in the neocortex using broader connections [23, 24]. Numerous studies have confirmed that when sleep is completely absent for 24 hours or when the duration is less than normal, a decline in alertness and changes in cognitive function is induced [25]. The consolidation of memories, which is also impaired by sleep loss and drowsiness, while the restriction of sleep (4 consecutive nights with 6 hours per night) similarly disrupts memory and leads to difficulties in transitioning from sleep to wakefulness [26].

Sleep and information reorganization: Researchers at the University of Freiburg in Germany have found that sleep can consolidate memory; however, their research showed that sleep cannot boost the creativity people need to solve problems. Memory consolidation and reorganization are two separate processes, and sleep does not accelerate memory reorganization, which is considered a prerequisite for creative thinking [27]. When individuals have a period of higher sleep quality, their mood improves, and at the same time, their memory function is better. In the process of sleep, the cerebral cortex will integrate short-term memories and long-term memories [28]. Complex information is integrated in the process of restructuring new nerve synaptic connections to consolidate and promote learning and memory. This process is conducive to effective recovery and is also very important for improving energy levels in the brain [18].

Active system integration: Memory storage occurs within two mutually independent systems, with encoded information pre-existing in the short-term memory storage center, the hippocampus, which constantly transfers short-term memories to the long-term memory center, the neocortex, which continuously consolidates and strengthens memories [29]. During wakefulness, the neocortex encodes information stored in the hippocampus, which is continuously reproduced, activated, and electroencephalographicall-y manifested as a dialog between the hippocampus and the neocortex [30]. Cortical slow waves drive hippocampal synchronization in the thalamus in a "top down" manner to generate the spike/spindle and sharp wave ripple complexes, and the synchronous emergence of the spike ripple enables hippocampal memory to be temporarily transferred into the cortical memory network, enabling the continuous transfer of short-term memory into long-term memory [31].

Sleep and synapses: An increase in synaptic strength creates more energy expenditure and larger synapses that occupy precious brain space. Downsizing the scale of synaptic connections during sleep may help save brain space and energy, which improves learning and memory. The number of synaptic terminals also decreases during sleep [32]. Persistent stimulation of neuronal synapses during wakefulness produces larger synapses, a phenomenon that plays an important role in memory and learning. According to research, to ensure that synapses do not become saturated and that neural signals and memory are not forgotten, this growth must be counteracted [33]. Sleep is considered a perfect counteracting modality, and it is ideal to have a resetting process during sleep hours. During sleep, synapses are balanced and restored. Research has shown that several hours of sleep reduced the synapse size by 18% in the two cerebral cortical regions tested [28]. Each night when we sleep, billions of synapses in the cerebral cortex shrink by approximately 20%. However, synaptic mRNA production is most likely only regulated by the circadian clock, independent of sleep quality. At notable daily time points (such as at dawn and dusk), mRNA automatically starts accumulating under the control of the circadian clock [31].

Hypnotic drugs and cognition: Arousal cycle alterations may interfere with cognition, leading to 0hippocampal-related cognitive deficits. The sleep/wake cycle is controlled by interactions between the sleep-promoting system, which includes inhibition of GABA activity, and the arousal-promoting system, which includes orexin, acetylcholine, and monoaminergic systems [34]. Emerging evidence suggests that Sleep Deprivation (SD) and Circadian Rhythm Disruption (CRD) may interact and increase the risk of Alzheimer's disease development. Both of these factors may damage intracerebral macromolecules (such as Aβ-like amyloid and microtubule-associated protein tau), increase local brain oxidative stress and reduce circulating melatonin levels [35]. After one night of high-quality sleep, individuals commonly feel clear-minded, and their performance in daily routines will decline if they do not obtain adequate sleep. There is a general concern that hypnotic drugs may impair physical and cognitive functions, causing muscle relaxation, ataxia, loss of balance, retrospective amnesia, attention deficits and slowed reaction times, and patients may temporarily lose mobility in response to hypnotic drugs and fail to respond appropriately [32], causing a fall or traffic accident. DORAs allow rapid induction and maintenance of sleep, improve perceived sleep quality, and have fewer effects on performance the following day during wakefulness. Animal experiments have shown that DORAs slightly promote cognition. The DSM scale is the most widely used cognitive screening scale, which comprehensively and rapidly reflects the intellectual status and cognitive decline of tested subjects [18]. It is also part of the revised Wechsler Adult Intelligence Scale, which assesses information processing, attention and psychomotor performance, and is used in memory research and clinical research [36]. Moreover, the DSM boasts a reputation for detecting the residual effects of hypnotics; it has been used for some tests of attention. Overall, DORAs appear to be promising as a good hypnotic option that does not impair cognition.

Dora and alzheimer disease

Interaction between sleep disorder and neurodegenerative disease (Alzheimer disease): Sleep deficiency and structural disruption leads to a reduction in the clearance of β Amyloid-Beta (Aβ) proteins and phosphorylated tau, exacerbating the formation of two major pathological features of Alzheimer's disease [37], namely, senile plaques and neurofibrillary tangles. The disease manifests as decreased cognitive function [38]. Therefore, early intervention in sleep disorders to delay pathological progression and cognitive impairment is an important strategy to address the challenge of Alzheimer's disease [39]. Patients with Alzheimer's disease clinically show frequent and prolonged episodes of daytime sleepiness, sleep-sustaining insomnia, sleep fragmentation, frequent arousal periods, and atypical early sleep patterns at night. In late Alzheimer's disease, sleep changes may lead to a virtual reversal of circadian sleep patterns and can be used as predictors of mortality and institutionalization, especially in patients with a sunset syndrome (i.e., aggravation of behavioural symptoms in the afternoon and evening) [1]. Sleep changes can be considered a marker of early Alzheimer's disease; individuals with sleep problems have a higher risk of developing preclinical Alzheimer's disease. Sleep structure and ageing sleep quality deteriorate with ageing [40]. Older adults have greater difficulties in initiating and maintaining sleep, manifested by longer sleep delays and more sleep fragmentation. As a result, they tend to spend more time awake (less total sleep) and have less sleep efficiency. Sleep disturbances may be associated with the development of Alzheimer's disease due to the reduction in non-REM sleep [4]. With age, the circadian rhythm also becomes weaker and less synchronized. Weaker circadian responses to external cues blur the line between sleep and arousal. Older people often become sleepy in the evening and may wake up too early to regain sleep [41]. Due to the impairment of the sleep-wake cycle, the frequency of daytime napping and excessive daytime sleepiness increases. Several studies have suggested that the circadian clock may regulate hippocampal-dependent learning [42]. A study using an animal model of jet lag showed that animals exposed to disrupted circadian cycles exhibited reduced hippocampal neurogenesis, impaired learning and memory, and increased haematological inflammatory markers, which also exacerbated the risk of Alzheimer's disease [39].

Dora affects sleep and reduces β and tau deposition: The release of orexin-a exhibited 24-hour fluctuations similar to that of the brain interstitial fluid.

Similar results were demonstrated in young, healthy subjects, with CSF Aβ concentrations that peaked early at night and were lower later in the night. CSF Aβ fluctuations disappeared after the formation of amyloid plaques in young patients with Alzheimer's disease with progenitor protein mutations [43]. In transgenic mice overexpressing a mutant human Amyloid Precursor Protein (APP), higher CSF Aβ concentrations were associated with wakefulness.

Orexin physiologically promotes arousal by inactivating monoaminergic groups and cholinergic networks during REM, while almorexant reduces Aβ plaques and tau formation and deposition in multiple brain regions of APP/PS1 (Alzheimer's disease) mice [44, 45]. The dysfunction of cholinergic neurotransmission in the neurodegeneration of Alzheimer's disease leads to upregulation of the orexin system [46]. It has been reported that orexin-A levels in the CSF are higher in patients with moderate to severe AD impairment and greater impairments of night time sleep, suggesting that orexin, as an important factor affecting sleep, may be involved in the process of cognitive impairment development in Alzheimer's disease [47, 48]. Patients with Alzheimer's disease often develop daytime sleepiness and take multiple naps, especially during the moderate-severe stages of the disease. Insufficient neurotransmission has been associated with an increased number of daytime naps and higher nocturnal sustained arousal in patients with Alzheimer's disease [4]. Correct orexin signaling is thought to be the key to ensuring appropriate physiological rhythms in the sleep-wake cycle and warrants further study in subjects at risk for Alzheimer's disease.

Future prospects of DORAs: Cognitive performance in Alzheimer's disease patients was negatively correlated with REM sleep latency and wake time after sleep onset and was positively correlated with sleep efficiency. Due to the complex relationship between amyloid, hyperorexin, and sleep wake and the clear role of dual-hyperorexin receptor antagonists in reducing β plaque formation in transgenic mice [49, 50], some researchers have hypothesized that prolonged loss of hyperorexin early in life may alter the balance between β production and degradation/clearance and then prevent or delay Aβ accumulation in the human brain [51]. We hypothesize that targeting the downregulation of orexin receptor antagonists as potential preventive, therapeutic, or neuroprotective agents for oretinergic systems is intended not only to manage AD sleep disorders [52] but also to slow AD neurodegenerative progression and cognitive impairment to improve sleep. However, the changes in sleep patterns from preclinical to clinical AD and the causal relationship between sleep patterns and AD are still unclear [53]. The neurobiological basis for explaining the relationship between sleep disturbance and cognitive decline/Alzheimer's disease remains to be elucidated.

Dora and narcolepsy/cataplexy

Possible causes of narcolepsy: Narcolepsy is a chronic sleep disorder of unknown cause mainly resulting from disturbed central regulation of arousal and sleep. The main manifestations of the disease are as follows:

- Intolerable drowsiness in the day.
- Sudden muscle tone loss (cataplexy) induced by emotional activity (euphoria and abulia) cataplexy).
- Hallucinations during sleep and
- The four cardinal signs of paralysis during sleep [54].

Narcolepsy patients are almost immediately able to transition from wakefulness to sleep with loss of muscle tone and associated falls and injuries, which may be accompanied by a short period of rapid eye movement sleep called cataplexy that can occur at any time of the day [24]. In addition, the occurrence of cataplexy is often and strongly associated with predisposing factors such as positive and/or negative emotions, stress, fatigue, and oversaturation [41]. DORAs tend to promote a disproportionate degree of rapid eye movement sleep, and there is a clear relationship between cataplexy and rapid eye movement sleep, which is mediated by "rapid eye movement" neurons in the dorsal tegmental nucleus that are not active during non-rapid eye movement sleep, presumably by "rapid eye movement off" neurons located in the periaqueductal grey matter [55], which in turn are controlled by the amygdala and the emotional state of the affected individual. When the amygdala is activated by intense emotion, rapid eye movement neurons are blocked, muscle tone is lost, and cataplexy occurs [56].

Association between DORAs and narcolepsy: Studies have been conducted in canine animal models with hereditary narcolepsy-like symptoms present with in vivo OX1 receptor gene abnormalities. In addition, orexin gene null mice can also develop narcolepsy-like sleep disorders. Within post-mortem brain tissue specimens from narcolepsy patients, a large decrease in the number of orexin-producing neurons has been observed. Low CSF orexin-A levels are the gold standard (highly specific and sensitive) for the diagnosis of NT1 (Narcolepsy Type I) [57, 58]. In NT1, an irreversible loss of orexin neurons, possibly due to autoimmune processes, leads to irresistible sleep transitions during the day (especially rapid eye movement sleep), difficulty in maintaining long periods of wakefulness, incomplete nocturnal sleep, frequent transitions between sleep stages, and increased arousals during sleep. The behavioural instability caused by orexin deficiency has been well studied in rodents [59]. Compared with wild-type mice, orexin knockout mice exhibit normal sleep and wakefulness but a very short NREM sleep cycle and more frequent transitions between states. Survival analysis of wakefulness episodes showed that orexin was necessary to maintain prolonged wakefulness episodes, and orexin deficiency had little effect on wakefulness episodes < 1 min [22]. The results of an in-human study also showed an association between CSF orexin levels and markers of nocturnal sleep stability (onset of sleep and wakefulness and sleep-wake transitions) in hypersomnic patients [21].

DORA application and sudden collapse: In narcolepsy-susceptible rodents, almorexant induced cataplexy episodes. Similar effects were observed with sb-649868 (a selective orexin OX1 and OX2 receptor antagonist). Whether this was related to the near irreversible ox1r antagonism carried by sb-649868 upon reaching equilibrium [60], the sudden massive blockade of orexin in the brain, the inability to maintain normal wakefulness and basic activity, and the subject's entry into overt sleep episodes remains to be determined. It is important to emphasize that the relatively low incidence of spontaneous cataplexy in pre-orexin KO mice, and even in dual receptor KO mice, may not occur unless the animals are highly stressed [61]. In related studies of symptoms recapitulating narcolepsy or cataplexy in susceptible populations, daily nocturnal dosing of suvorexant for 28 consecutive days also did not lead to adverse events consistent with episodic somnolence [62], particularly cataplexy (rapid eye movement sleep intrusion into wakefulness with sudden loss of muscle tone). DORAs also significantly reduced the latency of REM sleep, possibly indicating a narcolepsy-like change in sleep architecture [63]. More research is needed to determine whether DORAs cause narcolepsy-like symptoms. A study in Narcolepsy Type 1 (NT1) patients showed that chronic loss of orexin signaling may perturb a β balance between production and degradation/clearance [62, 64]; therefore, the risk of progression to Alzheimer's disease is likely to be reduced, as is the delayed appearance of amyloid plaques and associated disease symptoms.

Dora and depression

Insomnia and depression: Compared with individuals without sleep difficulties, individuals with insomnia have twice the risk of depression, and people with depression will be in a depressed and agitated environment for a long time, which will also affect the central nervous system of patients, insomnia, and up to 40% of insomnia patients will suffer from depression or anxiety. Insomnia and depression often have a mutually causal relationship [65, 66], and their onset in patients is often indiscernible; in fact, insomnia and depression share similar symptoms and are inextricably linked. The main symptoms of insomnia are early waking, difficulty falling asleep, ease of waking, and declines in daytime alertness (easy to be distracted, not awake). Meanwhile, depressed patients have a reduced ability for limbic structures (such as the amygdala) to downregulate brain activity during sleep [67]. This state of hyperexcitability is associated with hyperactivation of the Hypothalamic–Pituitary–Adrenal (HPA) axis and is supported by chronically elevated Central Nervous System (CNS) activation; it causes patients to have difficulty falling asleep, maintaining sleep, and waking up early in the morning [9, 29].

DORAs regulate moods: In addition to its role in regulating the sleep/wake cycle, orexin may also affect other pathways, including those related to arousal, anxiety, cognition and psychomotor tone, by altering arousal and energy balance. Animal models of stress and depression suggest that orexin-2 receptor antagonists may have an antidepressant-like activity [68]. Seltorexant exhibited antidepressant effects by improving core symptoms in patients with major depressive disorder and improving sleep efficiency in patients with insomnia. Excessive arousal plays an important role in the pathophysiology of Major Depressive Disorder (MDD). Seltorexant (jnj-

42847922/min-202, a selective antagonist of the human orexin-2 receptor ox2r, counteracts the effects of hyperexcitability by inappropriately releasing orexin at night, thus reducing depressive symptoms [69]. The apparent improvement in cognitive processing capacity and the improvement in central nervous system function indicate that there is a trend toward subjective improvement in patients' mood at the highest dose administered. This finding may indicate that the orexin system is involved in emotion regulation [70]. Studies have shown that the severity of depression is closely related to cognitive arousal and more disturbed sleep. There was a nonsignificant trend of a positive correlation between the improvement of depressive symptoms by seltorexant and the improvement of Sleep Quality (SE) [71, 72]. The orexin system is silent during nonrapid eye movement sleep, resuming activity during periods of wakefulness in sleep, and a more prolonged state of wakefulness is present in patients with major depression [73]. Seltorexant has been hypothesized to shorten these arousal periods, thereby improving overall objective and perceived sleep quality.

Response of Dora in clinical application: Treatment with seltorexant 20 mg has results in observations of a statistically significant and clinically meaningful reduction in depressive symptoms. In addition to its effects on subjective and objective sleep initiation and maintenance, suvorexant also improved patients' perceptions of sleep quality, becoming delirious and being refreshed in the morning [74, 75]; these effects may also be related to the action of DORAs on reward hubs, and the clinical benefits of nocturnal sleep improvement are reflected in patients' and clinicians' overall assessments of disease severity and improvement [70]. Overall, seltorexant treatment showed antidepressant effects on core depressive symptoms, with a trend toward improved patient self-reported sleep experiences [76]. Therefore, it is highly likely that multiple DORAs will be used concomitantly with antidepressant medications in the future as a safe combination treatment option for patients suffering from insomnia, depression and/or anxiety disorders.

Orexin and addiction

Harm of addiction: A study conducted by the World Health Organization in 2008 showed that approximately 40.5 million people worldwide have moderate or severe disease due to alcohol dependence. According to statistics, illicit drugs lead to an average loss of 19 years of life among users, smoking leads to an average loss of 5 years of life among users, and alcohol consumption leads to an average loss of 2 years of life among users [77, 78]. Addiction has become a worldwide health concern. Addiction is the act of compulsive, persistent demand for addictive substances and lack of control, which leads to alterations in central reward circuits in the brain [79]. The hypothalamus, an important brain region that regulates natural reward, specifically expresses orexin and hypocretin neuropeptides. In addictive behaviours, orexin neurons are activated, and they project mainly to the hypothalamic Paraventricular Nucleus (PVN), VTA and nucleus accumbens regions [80]. These neurons are involved in the emotional dysregulation that occurs during withdrawal, and stronger withdrawal symptoms have been associated with lower levels of orexin-A [81].

Cocaine addiction: The VTA is a major brain region involved in cocaine addiction, as well as one of the strongest orexin neuron projecting brain regions. Oxa activates the PKC → PLC signaling pathway via ox1r, which enhances N-methyl-D-aspartate receptor-mediated Excitatory Postsynaptic Currents (EPSCs) of dopaminergic neurons in the VTA [82].

Injection of the ox1r antagonist, SB-334867, into the VTA blocks the behavioural sensitizing effects associated with cocaine as well as the alterations in synaptic plasticity induced by long-term cocaine administration. Furthermore, in mice, systemic administration of the ox1r antagonist SB-334867 reduced cocaine-induced performance of Conditioned Place Preference (CPP) [83, 84]. Neither orexin peptide nor ox1r expression levels were affected by acute cocaine administration or sensitization experiments, but orexin mRNA levels were reduced in the hypothalamus [5]. Orexin increases the sensitivity of the body to the drug in patients with long-term cocaine administration, and its administration does not necessarily need to coincide with the effects of the drug itself.

Nicotine addiction: The brain regions mediating nicotine addiction are mainly located in the projection areas of the PVN and the insula of orexin neurons. Administration of SB-334867 into the insular cortex and PVN reduces nicotine self-administration and somatic withdrawal responses, respectively. Orexin knockout and sb-334867-pretreated mice did not show anxiety in response to high doses of nicotine [85, 86]. In addition, the expression of the FOS protein was enhanced in orexin neurons after nicotine withdrawal neurons were activated, and orexin also facilitates the process of nicotine reabsorption [87]. In conclusion, the function of orexin in the nicotine reward circuit is mainly reflected its reinforcement of nicotine self-administration and negative effects, such as exacerbating withdrawal syndrome, increasing anxiety and increasing the chance of relapse [88].

Morphine addiction: The VTA is an important site of action for morphine, and injection of orexin into the VTA and the pharmacological activation of orexin neurons in the lateral hypothalamus leads to the recapitulation of extinguished morphine CPP [89]. We found a positive correlation between FOS protein levels of orexin neurons in the lateral hypothalamus and CPP scores of morphine, cocaine, and food in mice. The amount of FOS protein expression in the nucleus accumbens and the score on the CPP of morphine were reduced in mice systemically administered SB-334867, but this change was not observed in the nucleus coeruleus or VTA [90, 91]. However, injection of SB-334867 into the locus coeruleus nucleus of mice reduced the somatic symptoms of morphine withdrawal, suggesting that orexin may be involved in different processes of the morphine withdrawal response in different brain regions [92].

Alcohol addiction: Orexin levels were positively correlated with drinking behaviour, and administration of DA1r agonists and DA2r agonists in the lateral hypothalamus elevated and decreased orexin mRNA levels in the lateral hypothalamus, respectively, and increased and decreased alcohol consumption, respectively, in mice. The chronic gavage of alcohol-consuming Sprague Dawley rats decreased the amount of orexin mRNA in all brain regions [93, 94], and acute alcohol administration increased the amount of orexin mRNA and orexin peptide in the lateral hypothalamus but did not increase the amount of orexin mRNA in the Dorsomedial Hypothalamus (DMH) or Perifornical Area (PFA) [95]. In conclusion, the role of orexin in modifying the rewarding effects of alcohol may differ depending on the mode of administration, whether it is administered alone, and whether it is administered chronically [96]. Orexin receptors also play important roles in drug addiction and reward-related behaviours, and orexin neurons that project to different brain regions also have different regulatory effects on addiction caused by different drugs. The regulation of the orexin signaling system will likely become an important approach for the treatment of addiction [97].

Conclusion

Previous studies investigating the biological and physiological roles of orexin have yielded remarkable results. The orexin system has a wide range of effects, not only promoting appetite and enhancing energy metabolism but also affecting sleep-awakening behaviours, learning and memory, food and drug addiction behaviours stress, cancer, the cardiovascular system, and the neuroendocrine and reproductive systems.

This review found that orexin can affect cognition by improving sleep and inhibiting the Alzheimer's disease process; taking an orexin double receptor antagonist does not relieve thirst; orexin can regulate mood and improve depression; and orexin seems to more effective than conventional drug treatments for addiction .

There is a growing body of evidence that orexin plays a role in the causative mechanisms of several disorders, with a bidirectional relationship in the pathophysiology of these diseases, raising the possibility of treatment with DORAs to improve the course of the disease. However, overall, the evidence for the efficacy of DORAs is scarce, and conflicting results have been reported. With further study of orexin signaling systems, it is reasonable to believe that more effective treatment options will be developed in the future and that better understanding of orexin signaling systems may lead to new ideas and methods to treat diseases.

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