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Orexin and Psychoneurobiology: A Hidden Treasure

*Hayder M. Alkuraishy, Ali I. Al-Gareeb
and Naseer A. Al-Harchan*

Abstract

Orexin is a neuropeptide secreted from the lateral hypothalamus and prefrontal cortex concerned in wakefulness and excitement. This study aimed to review the possible neurobiological effect of orexin. A diversity of search strategies was adopted and assumed which included electronic database searches of Medline and PubMed using MeSH terms, keywords, and title words. Orexin plays a vital role in activation of learning, memory acquisition, and consolidation through activation of the monoaminergic system, which affects cognitive flexibility and cognitive function. Orexin stimulates adrenocorticotrophin (ACTH) and corticosteroid secretions via activation of the central corticotropin-releasing hormone (CRH). Cerebrospinal (CSF) and serum orexin levels are reduced in depression, schizophrenia, and narcolepsy. However, high orexin serum levels are revealed in drug addictions. Regarding neurodegenerative brain diseases, CSF and serum orexin levels are reduced in Parkinson's disease (PD), Alzheimer's disease (AD), Huntington's disease (HD), amyotrophic lateral sclerosis (ALS), and multiple sclerosis (MS). Orexin antagonist leads to significant reduction of sympathetic overactivity during withdrawal syndrome. Also, orexin antagonist improves sleep pattern. The orexinergic system is involved in different psychiatric and neurological disorders; therefore targeting of this system could be a possible novel pathway in the management of these disorders. In addition measurement of CSF and serum orexin levels might predict the relapse and withdrawal of addict patients.

Keywords: orexin, sleep disorders, psychiatric disorders, neurodegenerative disorders

1. Introduction

Orexin, also known as hypocretin, is a neuropeptide that regulates arousal, wakefulness, and appetite. The most common form of narcolepsy, in which the sufferer experiences brief losses of muscle tone (cataplexy), is caused by a lack of orexin in the brain due to destruction of the cells that produce it. There are only 10,000–20,000 orexin-producing neurons in the human brain, located predominantly in the perifornical area and lateral hypothalamus. They project widely throughout the central nervous system, regulating wakefulness, feeding, and other behaviors. The orexin system was initially suggested to be primarily involved in the stimulation of food intake, based on the finding that central administration of orexin-A and orexin-B increased food intake. In addition, it stimulates wakefulness, regulates energy expenditure, and modulates visceral function [1, 2].

Two distinct types of orexin, orexin-A and orexin-B, were identified; they act on specific receptors called orexin receptor type 1 (OX1R) and orexin receptor type 2 (OX2R). Orexin-A activates both of these receptors equally, while orexin-B has a five times higher affinity to OX2R than OX1R. Upon activation, prepro-orexin will split to orexin-A and orexin-B, which act on their G protein-coupled receptors (**Figure 1**) [3].

Orexin receptors are distributed mainly in the lateral hypothalamus and adjacent areas, and their nerve fibers project to multiple brain regions. Orexinergic neurons in the lateral hypothalamus group are closely associated with reward-related functions. These neurons preferentially innervate the ventral tegmental area and the ventromedial prefrontal cortex. In contrast, the perifornical-dorsal group of orexinergic neurons is involved in functions related to arousal and autonomic response. These neurons project inter-hypothalamically, as well as to the brainstem, where the release of orexin modulates various autonomic processes. Indeed, accumulating evidence shows that the orexin/receptor system is ectopically expressed in several neurological disorders, suggesting that it plays an important role in the incidence and pathogenesis of these diseases [4].

It has been verified that hypothalamic orexigenic neurons are involved in reward functions, while prefrontal orexigenic neurons are linked in the regulation of autonomic and arousal functions. Moreover, orexin provokes and stimulates food intake via inhibition of autonomic digestive feedbacks. Orexigenic neurons are inhibited by leptin and food intake, while hypoglycemia and ghrelin activate orexigenic neurons. Amino acid and high-protein diets paradoxically provoke the hyperpolarization of orexigenic neurons and block glucose-induced orexigenic neuron activations [5]. Animal model studies have shown that orexin is a very important link between sleep and body metabolism since sleep deprivation leads to higher food intake and induction of catabolism [6].

Additionally, orexin stimulates different neurotransmitters which are linked to the activation of the central nervous system, including acetylcholine, histamine, noradrenaline, and dopamine. Therefore, mutations of orexin receptors lead to sleep disorders. Mice with orexin knockout are subjected to narcolepsy and excessive daytime sleepiness [7]. Alizamini et al. study showed that central

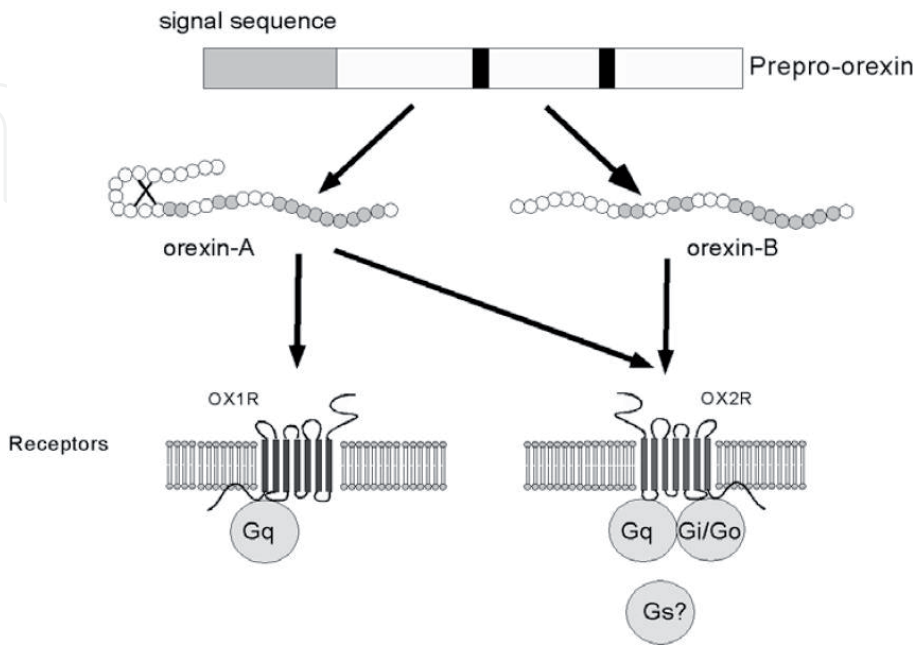


Figure 1.
Schematic representation of orexin system.

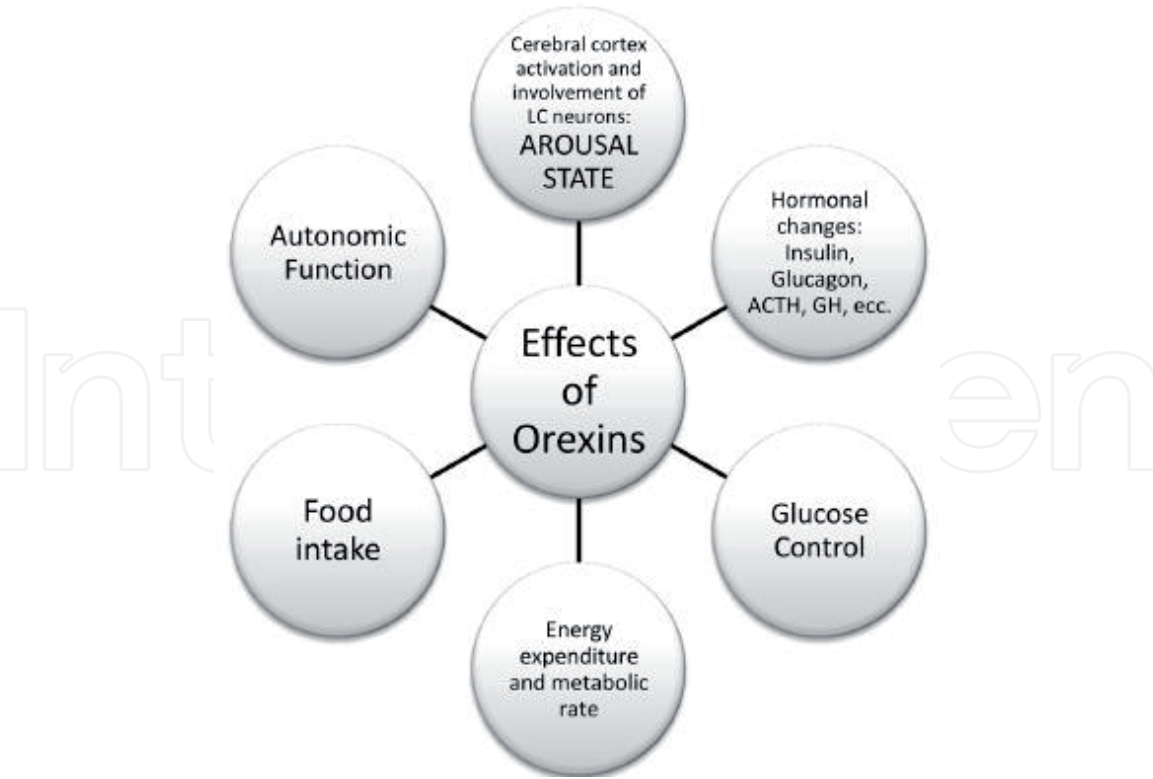


Figure 2.
Central and peripheral effects of orexin.

administration of orexin leads to stimulation of locomotion, psychomotor performance, body temperature, and energy expenditure. Furthermore, mice with orexin deficiency are subjected to obesity due to reduction of basal metabolic and energy expenditure rates. Beside, orexin knockout mice is characterized by a reduction in brown adipose tissue thermogenesis with poor differentiation of pre-adipocyte into adipocytes in the adipose tissue [8]. Central and peripheral effects of orexin are illustrated in **Figure 2**.

The aim of this study was to provide a narrative review of the neurobiological effect of orexin system and to examine the association between orexin neurotransmission and different psychoneurological disorders, including depression, schizophrenia, addiction, Parkinson’s disease, and dementia. Evidence from experimental, preclinical and clinical studies is evaluated for bidirectional relationships between orexin neurobiology and psychoneurological disorders. Given the nature of the subject area, it remains clear that this literature search cannot be regarded as a systemic review.

2. Method and search strategy

A diversity of search strategies was adopted and assumed which included electronic database searches of Medline and PubMed using MeSH terms, keywords, and title words. There is no limitation for publication year. The terms used for these searches were as follows: [orexin OR hypocretin] AND [cognitive function OR vigilance OR depression OR schizophrenia OR addiction OR Alzheimer dementia OR stroke OR sleep disorders]. [suvorexant OR orexin antagonists] AND [sleep disorders OR vigilance OR depression OR schizophrenia OR addiction]. Reference lists of identified and notorious articles were reviewed. Besides, only English articles were considered, and case reports were not involved in the review. The key

features of recognized relevant search studies were considered, and the conclusions were summarized in a narrative review.

2.1 Orexin and cognitive function

Orexin regulates behavioral and neuroendocrine response during stressful conditions as these events lead to the impairment of cognitive flexibility and function. Also, patients with psychiatric disorders such as panic disorder are associated with significant reduction of hypothalamic orexin activations [9].

It has been shown that stress improves male cognitive flexibility, but it worsens female cognitive flexibility due to gender differences in stress-induced orexin neuropeptide activations. Women are twice as likely as men to suffer from stress-related psychiatric disorders, such as post-traumatic stress disorder (PTSD) and major depressive disorder (MDD); however, the biological basis of these sex differences is not fully understood. Interestingly, orexins are known to be dysregulated in these disorders. Both preclinical and clinical studies have reported higher orexin system expression in females, which contributes to exaggerated neuroendocrine and behavioral responses to stress. Therefore, orexins may be important in the etiology of stress-related psychiatric disorders that present differently in men and women [10]. Piantadosi et al. illustrated that stimulation of prefrontal cholinergic neurons leads to the release of orexin from hypothalamic neurons, which play an important role in cognitive activation since high orexin activates the arousal state and executive functions via activation of cortical cholinergic neurons [11]. Chieffi et al. study reported the beneficial effects of exercise in stimulation of orexin release due to enhancement of hippocampal activity as exercise attenuates hippocampal deterioration and depressive symptoms in elderly persons through regulation of orexin release [12].

Notably, cognitive impairment is the main feature of neurological and neuropsychiatric disorders as in dementia and narcolepsy, which are linked to orexin dysfunction. Therefore, intranasal orexin peptide may be an effective agent for cognitive dysfunction [13]. Astonishingly, orexin plays a crucial role in activation of learning and memory, as orexin-A provokes memory acquisition and consolidation through activation of monoaminergic system. Consequently, orexin antagonist leads to significant memory dysfunction in the experimental rats [14]. Kim et al. study revealed that orexin is an important key factor of hippocampal neurogenesis as orexin-A participates in the hippocampal neuronal proliferation and neuroprotection following stroke; thus orexin agonist participates in prevention of negative stroke outcomes [15]. On the other hand, Uslaner et al. exhibited that dual orexin receptor antagonists (DORA-22) is an effective sedative agent, with less cognitive disability than GABA allosteric modulators, which cause significant cognitive dysfunctions [16, 17]. Therefore, orexin improves cognitive functions as illustrated in different human and animal studies (**Table 1**).

2.2 Orexin and neuroendocrinology

Orexin is involved in the regulation of central and peripheral signals to regulate metabolic homeostasis. Alongside, orexin stimulates adrenocorticotrophin (ACTH) and corticosteroid secretions via activation of central corticotropin-releasing hormone (CRH) and vasopressin. Therefore, orexin through OX2R receptor controls the hypothalamic-pituitary-adrenal axis (HPA) [18]. Previously, Malendowicz et al. illustrated that chronic orexin administration led to dose-dependent increase in cortisol and aldosterone plasma levels independent of ACTH levels, indicating a

| Species | Interventions | Results | References |
|--------------------|---|---|------------------------|
| Animals | Stimulation of prefrontal cholinergic neurons | ↑ orexin | Piantadosi et al. [11] |
| Humans and animals | Exercise Orexin-A administration | ↑ orexin Provokes memory acquisition and consolidation | Chieffi et al. [12] |
| Humans | Intranasal orexin-A administration | Improve cognition | Calva and Fadel [13] |
| Mice | Orexin-A administration | Stimulates angiogenesis and neuroprotection | Kim et al. [15] |
| Humans | Administration of orexin receptor antagonists | Stimulates angiogenesis and neuroprotection | Uslaner et al. [16] |

Table 1.
Orexin and cognitive functions.

direct stimulating effect of orexin on the adrenal cortex [19]. But in spite of these findings, Patel et al. study confirmed insignificant effect of orexin antagonists on ACTH and cortisol serum levels as well as on the markers of the sympathetic nervous system [20].

It has been reported that orexin administration leads to significant suppression of the hypothalamic prolactin release, which is not upturned by dopamine receptor antagonists like metoclopramide suggesting a novel pathway in controlling of prolactin secretion. The mechanism of prolactin inhibition may be through inhibition of prolactin-releasing factor or stimulation of prolactin-inhibiting factor. But previous study illustrated insignificant effect of orexin antagonist on prolactin plasma levels [21, 22].

Many studies showed that the blood glucose is regulated by central orexin through regulation of hepatic glucose production, skeletal glucose consumption and thermogenesis. High orexin or dysrhythmic in orexin secretion is linked with the development of obesity and insulin resistance [23, 24]. Thus, suvorexant and other orexin antagonists are effective in the management of obesity and insulin resistance via amelioration of body adiposity and augmentation of energy expenditure that improve glucose metabolism. Moreover, orexin-A has important roles in the regulation of pancreatic islet biology through activation of insulin secretion and prolongation of pancreatic islets life span [25].

Tsuneki et al. study illustrated that suvorexant improves glucose tolerance through inhibition of hepatic gluconeogenic factors, when administrated at resting time. However, administration of suvorexant at awaking time illustrates insignificant effect on glucose tolerance due to differential effects on the orexin sleep/wake operating system [26].

In addition, Flores et al. study illustrated an interaction between endocannabinoid and orexigenic neurons as there is a similarity between OX1R and CB1 receptors with diffuse overlapping in the anatomical distribution of these neurons. Therefore, the pharmacological effect of cannabinoid may be through orexigenic receptors [27]. The neuroendocrine effects of orexin are summarized in **Table 2**.

2.3 Orexin and psychiatric disorders

2.3.1 Orexin and depression

Among important etiological factors involved in the pathophysiology of depression, disturbances of monoamines and HPA are the main mechanistic pathways

| Species | Interventions | Results | References |
|--------------------|--------------------------------------|--------------------------------|---------------------------------------|
| Animals | Orexin administration | ↑ ACTH, cortisol | Czerwinska et al. [18] |
| Animals | Orexin administration | ↑ cortisol, aldosterone | Malendowicz et al. [19] |
| Humans | Orexin administration | No effect on ACTH and cortisol | Patel et al. [20] |
| Humans and animals | Orexin administration | Inhibits prolactin | Lyons et al. [21], Samson et al. [22] |
| Humans | High orexin levels | Insulin resistance and obesity | Gupta et al. [23], Cigdem et al. [24] |
| Humans and animals | Orexin administration | ↑ insulin secretion | Mediavilla and Risco [25] |
| Animals | Administration of orexin antagonists | Improves glucose tolerance | Tsuneki et al. [26] |

Table 2.
Neuroendocrine effects of orexin.

leading to functional disorders of neuroplasticity, which is regarded as a cardinal step in the onset of depression [28].

Diurnal variation in orexin serum levels revealed that high orexin levels are occurring at the middle of night. It has been reported that orexin level is significantly decreased in patients with depression in comparison with healthy subjects [29]. But paradoxical high orexin serum levels are seen in some depressed patients, which is normalized by selective serotonin reuptake inhibitors. Since, orexin-A CSF levels are negatively correlated with depressive symptoms [30].

Long-term antidepressant agents improve orexin serum levels regardless of the type of antidepressant medications [31]. Nevertheless, there are different findings concerning orexin levels in depression. Feng et al. reported that depression is linked to reduction of serotonergic neuronal activity which is responsible for modulation of orexinergic activity [32]. Thus reduction of serotonergic neuronal activity leads to activation of orexin neuroactivity leading to depression. However, orexin levels are significantly reduced in depression compared with healthy control [33].

The initial animal model study observed reduction in the orexinergic neurons by 18% with diminution in size of these neurons in comparison with normal rats. As well, prepro-orexin mRNA expression and orexin-A were reduced compared with control [34].

Previous preclinical study revealed a strong connection between low orexin and risk of depression which are inconsistent with previous studies that illustrated hypoactivity of orexinergic neurons in patients with depression since short-term antidepressant therapy improves sleep pattern through increasing and decreasing the expression of mRNA of orexin-A and orexin-B, respectively [35].

Ito et al. showed that administration of orexin-A leads to significant reduction of despair behavior in depression with important hippocampal neurogenesis via upregulation of neuropeptide Y (NPY). These changes are inhibited by co-administration of orexin-A antagonist [36].

Therefore, orexin levels are different according to the pathophysiology of depression. Low orexin in depressed patients is associated with hypersomnia, whereas high orexin in depressed patients is associated with insomnia and interrupted sleep [17]. Ji et al. illustrated that orexinergic neurons have direct connection to the ventral pallidum (VP) which is concerned with stress response and rewarding system. Orexin stimulates the VP and prevents depressive behavior. Therefore, high orexin in the VP is associated with elevated serum corticosterone serum levels

during acute stress, which per se prevent a depressive reaction against stressful events through improvement of stress resilience [37].

2.3.2 Orexin and schizophrenia

The association between orexin and schizophrenia had not been previously explored precisely [38]. Clinical and preclinical findings proposed that orexin and orexin agonist are of great value and useful in treating cognitive deficit in schizophrenia [39]. There are widespread connection and interaction between orexin and dopaminergic neurons in midbrain, thalamocortical region, and amygdala suggesting the potential role of orexinergic neurons in schizophrenia [40].

Modafinil is an atypical dopamine reuptake inhibitor used in the treatment of narcolepsy and antipsychotic drug-induced sleep disorder (**Figure 3**) [41]. Modafinil has been revealed as a complement of drugs in therapy of schizophrenia, and it reduce negative symptoms with no effect on the positive symptoms. Modafinil improves locomotor and psychomotor performances through activation of orexinergic neurons [42].

Therefore, activations of orexinergic neurons by modafinil may be an imperative step for future antipsychotic medications. These findings document that dopaminergic agonists mainly at D1 and D2 receptors modify orexinergic neurotransmissions [43]. Also, dopamine antagonists that cause weight gain lead to activation of orexin pathway, but dopamine antagonists which do not cause weight gain do not activate orexin pathway [44]. Nevertheless, amphetamine which indirectly activates dopamine leads to activation of orexinergic neurotransmission despite induction of weight loss. Moreover, clozapine activates only orexinergic neurons in the prefrontal cortex [45]. Similarly, orexin antagonists abolish olanzapine and haloperidol effect on midbrain dopaminergic neurons, suggesting that orexin is an important neurotransmitter mediates the action of antipsychotic drugs [46]. As well, Chen et al. illustrated that orexin-A is stimulated and upregulated by non-obese genic antipsychotic drugs [47]. Also, the high orexin level in patients with schizophrenia treated with antipsychotic drugs is regarded as a protective factor against the development and risk of drug-induced metabolic syndrome [48]. Furthermore, orexin agonist like modafinil ameliorates cognitive function, attention, and antipsychotic-induced sedation.

2.3.3 Orexin and addiction

The orexinergic system has broad projections and connections to different brain area which are concerned with drug-induced neuro-adaptation, including midbrain dopaminergic neurons, ventral tegmental area (VTA), nucleus accumbens (NA),

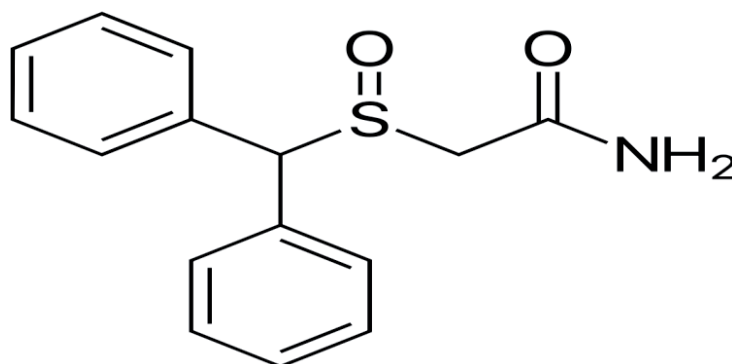


Figure 3.
Chemical structure of modafinil.

amygdala, and medial prefrontal cortex (mPFC). Drug abuse leads to augmentation of dopaminergic activity in NA through activation of orexinergic neurons at mesocorticolimbic pathway [49]. Correspondingly, experimental studies illustrated that OX1R and OX2R are highly expressed in the NA leading to inhibitory effect instead of excitatory effects seen on the VTA, amygdala, and mPFC. Therefore, a differential effect of orexin is receptor type dependent [50].

Acute administration of addicting drugs such as methamphetamine, nicotine, and amphetamine leads to activation of orexinergic neurons at the lateral hypothalamus. However, acute administration of cocaine and morphine does not affect orexinergic neurons. Besides, chronic administration of addict drugs causes activation of orexinergic neurons mainly at OX2R receptors, but chronic increasing dose of addict drugs leads to downregulation of orexinergic receptors [51]. Carr and Kalivas reported that orexin is an important mediator which enables cocaine to induce addiction-like behavior in rats due to dopaminergic neuronal changes [52]. Also, James et al. verified that orexinergic neurons at the lateral hypothalamus play a vital role in expression of addiction-like phenotype [53]. Thus, the orexinergic system is regarded as an important novel target for drug therapies to treat addiction.

Orexin serum level in chronic smoker subjects is related to craving in the phase of abstinence since it increased during addiction phase and reduced during withdrawal phase. This reduction leads to increase in craving and risk of relapse [54]. Therefore, orexin serum level is regarded as a potential biomarker predicts time and risk of smoking relapse.

Furthermore, Tsai and Huang reported that the orexin serum level is increased in heroin addicts who shifted to methadone maintenance therapy compared with controls suggesting that methadone increases orexin serum levels [55]. Similarly, orexin serum level is increased in chronic alcoholism, which is positively correlated with the severity of alcohol withdrawal. Alleviation of alcohol withdrawal syndrome is linked with reduction of the orexin serum level, which monitors the status of alcoholic patients during the abstinence period [56].

2.3.4 Orexin and sleep disorders

Narcolepsy is a sleep disorder that causes excessive daytime sleepiness or an intractable urge to sleep in, in which duration of rapid eye movement sleep (REM) is reduced. Cataplexy is a sudden reduction in muscle tones with preserved consciousness. Narcolepsy is commonly associated with cataplexy, which is triggered by emotional stimuli [57]. Methylphenidate, modafinil, and other psychostimulants are effective in the management of these sleep disorders [58]. Dysregulation of NREM sleep leads to narcolepsy only, whereas dysregulation of REM sleep leads to combined narcolepsy with cataplexy [59]. It has been reported that orexin increases vigilance through increasing awaking time and decreasing REM and NREM sleep periods. Both OX1R and OX2R are involved in the maintenance of arousal state directly or indirectly through the activation of monoaminergic neurons (noradrenalin, dopamine, histamine, and serotonin). Also, orexin activates cholinergic neurons in the basal forebrain, which is also important for arousal states [60]. Yamanaka et al. study illustrated that activation of OX2R by orexin leads to wakefulness which is mediated by a histamine neurotransmitter since antihistamine blocks the excitatory effect of orexin, while activation of OX1R by orexin leads to wakefulness, through noradrenalin neurotransmitter [61]. Reduction of orexin level in the cerebrospinal fluid was documented in patients with narcolepsy and nowadays is regarded as one of the diagnostic criteria in the diagnosis of narcolepsy.

Likewise, human postmortem study found that orexin peptide and prepro-orexin mRNA are deficient in the pons and cerebral cortex [62]. Therefore, these findings unveil that orexin is an important neuropeptide in the regulation of sleep and consolidated wakefulness. **Table 3** summarized the potential role of orexin in common psychiatric disorders.

2.4 Orexin in neurodegenerative diseases

2.4.1 Parkinson’s disease

Orexinergic neurons are severely affected in Parkinson’s disease (PD); previously Fronczek et al. confirmed that orexinergic neuron density was reduced in the prefrontal cortex by 40% with significant reduction in CSF orexin levels in PD patients compared to the healthy control [63].

Furthermore, animal model study illustrated that 15% damage to the orexin-ergic neurons did not affect CSF orexin, while damage more than 70% leads to 50% decline in the CSF orexin [64]. These findings may explain the association of narcolepsy with PD since both dopamine and orexin interplay in the regulation of sleep pattern through activation of midbrain and thalamocortical pathway [65]. Feng et al. illustrated that in PD, there is a deficiency in hypoxia inducible factor 1 alpha (HIF1- α) due to mitochondrial dysfunction and the administration of orexin-A leads to significant neuroprotective effect on the dopaminergic neurons through the activation of HIF- α [66].

Moreover, orexin-A improves dopaminergic neurons in PD through the reduction of tyrosine hydroxylase (TH) and activation of brain-derived neurotrophic factor (BDNF) in the substantia nigra [43]. Therefore, orexin antagonist may increase risk of PD due to reduction of the neuroprotective and stimulating effects on the dopaminergic neurons at substantia nigra [67]. Sheng et al. found that orexin plays important roles in activation of the subthalamic nucleus which may give a new evidence for the participation of the subthalamic orexinergic system in PD. Importantly, orexin-A increased the protein level of brain-derived neurotrophic factor in dopaminergic neurons of the substantia nigra. The upregulation of BDNF is mainly via OX1R [68]. Long-term therapy with ropinirole in PD leads to significant reduction in the orexin activity which might explain the adverse effect of ropinirole-induced sleep disorder through inhibition of glutamatergic excitatory effect on the orexinergic neurons. Therefore, pharmacotherapy of PD should be re-evaluated in this context [69].

| Psychiatric disorders | Species | Orexin levels | References |
|-----------------------|---------|---------------|---------------------|
| Depression | Human | Decreased | Kok et al. [29] |
| | Human | Increased | Grady et al. [30] |
| Schizophrenia | Human | Decreased | Mereu et al. [42] |
| | | | Patel et al. [20] |
| Chronic smoking | Animals | Increased | Al’Absi et al. [54] |
| Drug addictions | Human | Increased | James et al. [53] |
| Alcoholism | Human | Increased | Pan et al. [56] |
| Narcolepsy | Human | Decreased | Gabelle et al. [62] |

Table 3.
Orexin and psychiatric disorders.

2.4.2 Alzheimer's disease

Alzheimer's disease (AD) is a neurodegenerative disease affecting different brain areas characterized by cognitive deficit and progressive memory loss [70]. AD also affects hypothalamic orexinergic neurons leading to excessive daytime sleepiness, which is correlated with low orexin CSF levels, as reduction 40% of the brain cell number is linked with a 14% reduction in orexin CSF levels [71]. Normally, orexin regulates cholinergic and monoaminergic neuron firing during sleep and wakefulness. In AD a reduction in the cholinergic pathway leads to disturbance in sleep patterns leading to daytime sleepiness and insomnia at night which are a hallmark of sleep rhythm in AD [72]. Besides, reduction of cholinergic activity causes overactivity of orexinergic neurons, which causes abnormal sleep and cognitive functions. These changes lead to an elevation of the orexin CSF level, which is linked with reduced REM sleep [73].

Dementia with Lewy bodies is characterized by an elevation in α -synuclein level, which is accumulated in orexin-containing neurons at the hypothalamus causing interference in orexin axonal transport. This effect leads to a reduction in the activity of the orexinergic system in dementia with Lewy bodies but not in AD [74]. Therefore, there are complexities in the orexinergic system according to the clinical presentation and sleep pattern in patients with AD.

2.4.3 Huntington's disease

Huntington's disease (HD) is a hereditary neurodegenerative disorder characterized by personality changes, motor disturbances, cognitive decline, and weight loss [75]. HD is caused by a defect in the gene encoding huntingtin, a protein with unclear function, which is essential for cell survival during development and in adult life [76]. In HD there is neurodegeneration involving the neostriatum and cerebral cortex, with the manifestation of intraneuronal aggregates of misfolded huntingtin. Moreover, in patients with end-stage HD, there is about 90% of neuronal loss in the tuber nucleus of the lateral hypothalamus. Orexin-A and orexin-B are synthesized from the same precursor gene and are expressed in the same neurons with their cell bodies concentrated to the lateral hypothalamus [77]. Preclinical and clinical studies observed that orexin serum and CSF levels are decreased by 72% in HD. In healthy subjects, orexin CSF level is $>200\text{pg/ml}$, but in HD and narcolepsy, this level is decreased below 110pg/ml , due to degeneration of orexinergic neurons in the lateral hypothalamus. Therefore, CSF orexin level is regarded as a biomarker to evaluate the disease progression and usefulness of therapeutic intervention in patients with HD [78, 79]. However, Meier et al. illustrated that CSF and serum orexin levels are of no diagnostic value in prediction and follow-up of HD [80].

Recently, Cabanas et al. observed that orexin in HD has aberrant effects leading to abnormal sleep pattern, and thus orexin antagonist suvorexant may be of great value in restoring normal sleep and behavioral disturbance in HD [81] in addition, these neurons remain functional and illustrate paradoxical effect, it become more modifiable and affect by serotonin and noradrenaline, and less sensitive to the effect of suprachiasmatic nucleus (the master clock of the brain) causing abnormal biological circadian rhythm [81, 82].

Therefore, orexin level in HD is reduced, but the remaining functional orexinergic neurons lead to abnormal circadian biological rhythm causing behavioral, motor, and sleep disturbances.

2.4.4 Multiple sclerosis

Multiple sclerosis (MS) is a demyelinating disease in which the insulating covers of nerve cells in the brain and spinal cord are damaged. This damage disrupts the ability of parts of the nervous system to transmit signals, resulting in a range of signs and symptoms, including physical, mental, and sometimes psychiatric problems. Specific symptoms can include double vision, blindness in one eye, muscle weakness, and trouble with sensation or coordination. MS takes several forms, with new symptoms either occurring in isolated attacks (relapsing forms) or building up over time (progressive forms). Between attacks, symptoms may disappear completely; however, permanent neurological problems often remain, especially with the advancement of the disease [83, 84].

The three main characteristics of MS are the formation of lesions in the central nervous system, inflammation, and the destruction of myelin sheaths of neurons. These features interact in a complex and not yet fully understood manner to produce the breakdown of nerve tissue and in turn the signs and symptoms of the disease. Cholesterol crystals are believed to both impair myelin repair and aggravate inflammation. MS is believed to be an immune-mediated disorder that develops from an interaction of the individual's genetics and as yet unidentified environmental causes. Damage is believed to be caused, at least in part, by attack on the nervous system by a person's own immune system [85].

Considering the multiplicity of symptoms associated with multiple sclerosis (MS), there is possibility that hypocretin system function might be involved in the pathogenesis of the disease. Papuc et al. showed that high orexin CSF level in patients with MS as compared with healthy controls, but it positively correlated with fatigue level, suggesting a compensatory mechanism for the production of orexin in MS [86]. On the other hand, Nozaki et al. illustrated that orexin CSF level is reduced and correlated with symmetrical hypothalamic lesion and spinal cord damage in MS. Therefore, low orexin level was implicated in the pathogenesis of hypersomnia and cognitive deficit in patients with MS [87]. Recently, Pallais et al. confirmed that orexin has a neuroprotective effect in MS through inhibition of inflammatory and proinflammatory mediators mainly matrix metalloproteinases (MMP-3, MMP-9) which are involved in damage of neuronal matrix proteins. Consequently, low CSF orexin level indicates underlying active disease [88].

Therefore, CSF orexin level is a valuable biomarker in the diagnosis and prediction of the severity of MS.

2.4.5 Amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis (ALS), also known as motor neuron disease (MND), is a disease that leads the death of neurons controlling voluntary muscles. The underlying mechanism involves damage to both upper and lower motor neurons. ALS is characterized by stiff muscles, muscle twitching, and muscle weakness is still unknown. The cause of ALS is not known in 90% of cases but is believed to involve both genetic and environmental factors. The remaining 10% of cases is inherited [89]. Previously, Van Rooij et al. illustrated that CSF orexin level was normal in patients with ALS and not correlated with age and gender. However, a disturbance in the orexinergic system is involved in the pathogenesis of ALS [90]. Moreover, the pathogenesis of ALS is associated with lateral hypothalamic lesions, a site of the orexinergic system leading to sleep disturbances and hypersomnia [91].

Despite different and large body of literature survey, little is known about CSF orexin levels, in clinical and preclinical studies in ALS.

Therefore, orexin CSF level and orexinergic activity in different neurodegenerative diseases are summarized in **Table 4**.

2.5 Orexin antagonists and neurobiology

Regarding orexin antagonists, suvorexant is a dual orexin receptor antagonist was approved by the Food and Drug Administration (FDA) on 13 August 2014 [92]. Other orexin antagonists are almorexant, lemborexant, and filorexant are used in the management of insomnia and other sleep disorders. Also, these drugs may be of great value in the control of depressive disorders and peripheral diabetic neuropathy [93].

Suvorexant (**Figure 2**) is the first orexin antagonists approved in the United States for treatment of insomnia, which is effective in reduction of time to sleep onset and increase of total sleeping time [94]. Moreover, administration of SB-33867 which is an orexin antagonist leads to significant reduction of sympathetic tone causing a reduction in blood pressure, heart rate, and plasma noradrenalin. These findings suggest that orexin through OX1 receptor regulates sympathetic tone since intravenous administration of orexin leads to parallel increases in noradrenalin plasma levels [95].

Hatta et al. study confirmed the significant effect of suvorexant in the management of delirium in elderly patients in acute care units. The anti-delirium effect is due to the regulation of circadian biology [96]. Delirium is proposed to be related of suvorexant to disturbances and disorders in sleep pattern in critically ill patients in the intensive care unit. Also, attention disorders are caused by disturbances in the ascending reticular activating system (ARAS) which is responsible for maintenance of human arousal. Normally, the arousal state is regulated and stimulated by ARAS neurotransmitters and by hypothalamic orexin [97]. Therefore, orexin receptor antagonists may play important role in the regulation of hypothalamic and brain stem stress during acute injury. Moreover, a recent study by Kawada et al. illustrated that suvorexant add-on therapy to ramelteon in the management of sleep disorders in patients with acute stroke is more effective than when combined with benzodiazepines [98].

It has been verified that prolonged alcohol consumption is associated with sleep disturbance which is a powerful factor for relapse and setback to alcohol use. Suvorexant reduces the motivation properties of alcohol, so it plays a crucial role in the prevention of alcoholism [99].

Beside, Gentile et al. study revealed the possible role of suvorexant in reduction of motor impulsivity of cocaine-induced psychostimulant effects. Thus suvorexant may be effective in attenuation of cocaine withdrawal syndrome [100].

As well, suvorexant had placebo-like effect on EEG in comparison with zolpidem which has a significant reduction in the spectral density of rapid eye movement and non-rapid eye movement sleep (NREM) pattern [101].

| Psychiatric disorders | Species | CSF orexin levels | References |
|-----------------------|---------|-------------------|-----------------------|
| Parkinson's disease | Human | Decreased | Fronczek et al. [63] |
| Alzheimer's disease | Human | Increased | Liguori et al. [73] |
| Huntington's disease | Human | Decreased | Mignot et al. [78] |
| | Animals | Normal | Papuc et al. [86] |
| Multiple sclerosis | Human | Decreased | Nozaki et al. [87] |
| ALS | Human | Normal | Van Rooij et al. [90] |

Table 4.
Orexin and neurodegenerative diseases.

In spite of the wide uses of suvorexant in the management of sleep disorders and controlling insomnia, it did not reduce the psychomotor performances as documented by Vermeeren et al. study [102].

Orexin-A is involved in regulation of feeding; it stimulates nocturnal feeding through OX1 receptor. Therefore, OX1 receptor antagonist regulates feeding and reduced nocturnal feeding; thus, orexin antagonist could be useful in the treatment of obesity [103]. Orexin-A is implicated in the pathogenesis of obesity; it promotes hyperphagia through central activation of cannabinoid receptors and inhibition of melanocyte-stimulating hormone [104]. Both orexin-A and endocannabinoid increases glucose response of neuronal excitability in the arcuate nucleus leading to induction of feeding and obesity [104].

In summary, more research is required to reinforce the extant information on the importance of the limited number of factors studied to date and provide data on additional potentially relevant effects. Similarly, rubric for such research should shift from preclinical and animal model studies to clinical studies to illustrate disease progression and treatment effects in relation to orexin neurobiology. This study suggests that orexin system is a future target in the management of different psychoneurological disorders after delineating the specific role of orexin receptor agonists and antagonists. Moreover, measurement of orexin serum level which is an easy method may be of great value in evaluation and assessment of different neurological disorders. Also, ratio of orexin serum level/CSF orexin level may reflect the activity of endogenous orexinergic system.

3. Conclusion

Orexin system is regarded as a potential novel target in the management of schizophrenia, depression, addiction, and sleep disorders. Orexin serum level might predict relapse and withdrawal of addict patients.

Conflict of interest

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Author details

Hayder M. Alkuraishy*, Ali I. Al-Gareeb and Naseer A. Al-Harchan
Department of Clinical Pharmacology, Medicine and Therapeutic, Medical Faculty,
College of Medicine, Al-Mustansiriya University, Baghdad, Iraq

*Address all correspondence to: hayderm36@yahoo.com

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