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# Involvement of orexinergic system in psychiatric and neurodegenerative disorders: A scoping review

Hayder M. Al-Kuraishy, May H. Abdulhadi, Nawar R. Hussien, Marwa S. Al-Niemi, Huda A. Rasheed, Ali I. Al-Gareeb

## Abstract:

Orexin is a neuropeptide secreted from lateral hypothalamus and pre-frontal cortex concerned in the 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 during the search. Orexin plays a vital role in activation of learning, memory acquisition, and consolidation through activation of monoaminergic system, which affect cognitive flexibility and cognitive function. Orexin stimulates adrenocorticotropin and corticosteroid secretions via activation of central corticotropin-releasing hormone. Cerebrospinal fluid (CSF) and serum orexin serum 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 serum levels are reduced Parkinson disease, Alzheimer dementia, Huntington's disease, amyotrophic lateral sclerosis, and multiple sclerosis. Orexin antagonist leads to significant reduction of sympathetic over-activity during withdrawal syndrome. As well, orexin antagonist improves sleep pattern. Orexinergic system is involved in the different psychiatric and neurological disorders; therefore, targeting of this system could be 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:

Addiction, depression, learning, memory, orexin, schizophrenia, sleep disorders

## Introduction

### Orexigenic system

Orexin is a neuropeptide secreted from orexigenic neurons at hypothalamus and prefrontal cortex in about 10,000–20,000 neurons.<sup>[1]</sup> Orexin is responsible for the regulation of weak fullness and arousal, which was discovered in rat brain in 1998 by two researcher groups, one name it hypocretin, since it produced from hypothalamus, and the second group called it orexin from the orexin Greek word which means appetite.<sup>[2]</sup>

Two distinct types of orexin, orexin-A and orexin-B, were identified with 50% similarity, they act on specific receptors which are orexin receptor type 1 (OX1R) and orexin receptor type 2 (OX2R) receptors. Orexin-A activates these equally, while orexin-B has a higher affinity to (OX2R) than (OX1R) [Figure 1].<sup>[3]</sup>

Orexin receptors are distributed mainly in the lateral hypothalamus and adjacent areas; 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

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Department of  
Pharmacology, Toxicology  
and Medicine, College of  
Medicine Almustansiriya  
University, Baghdad, Iraq

### Address for correspondence:

Dr. Hayder M. Al-Kuraishy,  
Department of  
Pharmacology, Toxicology  
and Medicine, College of  
Medicine Almustansiriya  
University, P.O. Box:  
14132, Baghdad, Iraq.  
E-mail: hayderm36@  
yahoo.com

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prefrontal cortex (mPFC). 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 different neurological diseases.<sup>[4]</sup>

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, and stimulated by hypoglycemia and ghrelin. Amino acid and high protein diets paradoxically block glucose-induced orexigenic neuron activations.<sup>[5]</sup> Animal model studies have shown that orexin link sleep with the body metabolism, since sleep deprivation leads to higher food intake and induction of catabolism.<sup>[6]</sup>

Moreover, orexin stimulate different neurotransmitters which are linked to the activation of 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.<sup>[7]</sup> Alizamini *et al.*'s study showed that central administration of orexin leads to stimulation of locomotion, psychomotor performance, body temperature, and energy expenditure. Furthermore, mice with orexin deficient are subjected to obesity due to reduction of basal metabolic and energy expenditure rates. Beside, orexin knockout out mice is characterized by a reduction in brown adipose tissue thermogenesis with poor differentiation of preadipocyte into adipocytes in the adipose tissue.<sup>[8]</sup> Central and peripheral effects of orexin are illustrate in Figure 2.

The aim of this study article was to provide a narrative review of the neurobiological effect of orexin system

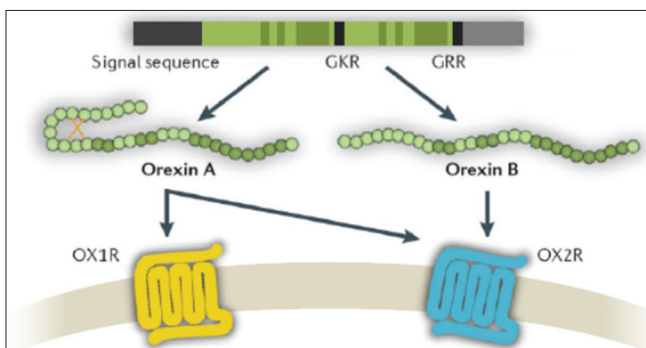


Figure 1: Schematic representation of orexin system

and to examine the association between orexin neurotransmission and different psychoneurological disorders, including depression, schizophrenia, addiction, Parkinson disease (PD), and dementia. Evidence from experimental, preclinical, and clinical studies is evaluated for the relationships between orexin neurobiology and psychoneurological disorders.

### Search strategy

A diversity of search strategies including; electronic database searches of Medline and Pubmed using MeSH terms, keywords and title words during the search. 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 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 summarized in a narrative review.

### Role of orexin in vigilance and cognitive function

Orexin regulates behavioral and neuro-endocrine response during stressful conditions as these events lead to the impairment of cognitive flexibility and cognitive function. As well, patients with psychiatric disorders such as panic disorder are associated with significant reduction of hypothalamic orexin activations.<sup>[9]</sup>

It has been shown, 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 posttraumatic stress disorder and

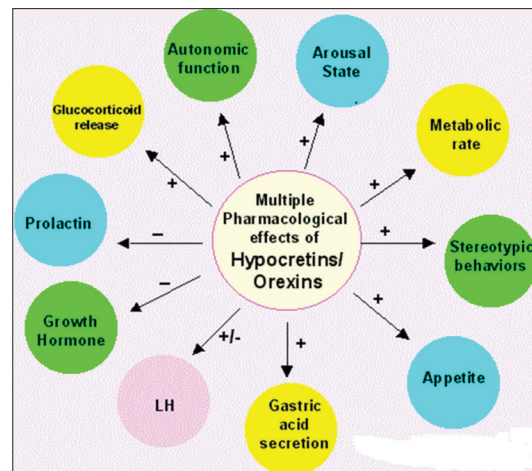


Figure 2: Central and peripheral effects of orexin

major depressive disorder; 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.<sup>[10]</sup> Piantadosi *et al.* illustrated that stimulation of prefrontal cholinergic neurons lead 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.<sup>[11]</sup> Chieffi *et al.*'s 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.<sup>[12]</sup>

As well, cognitive impairment is the main feature of neurological and neuropsychiatric disorders as in dementia and narcolepsy. Therefore, intranasal orexin peptide may be an effective agent for cognitive dysfunction.<sup>[13]</sup> 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.<sup>[14]</sup> Kim *et al.*'s 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 the prevention of negative stroke outcomes.<sup>[15]</sup> On the other hand, Uslaner *et al.* exhibited that dual orexin receptor antagonists-22 is an effective sedative agent, with less cognitive disability compared with GABA allosteric modulators, which cause significant cognitive dysfunctions.<sup>[16,17]</sup>

### Endocrine effects of orexin

Orexin is involved in the regulation of central and peripheral signals to regulate metabolic homeostasis. Alongside, orexin stimulates adrenocorticotropin (ACTH) and corticosteroid secretions via activation of central corticotropin-releasing hormone, and vasopressin. Therefore, orexin through OX2R receptor controls hypothalamic-pituitary axis (HPA).<sup>[18]</sup> Malendowicz *et al.* illustrated that a chronic orexin administration led to dose-dependent increased in cortisol and aldosterone plasma levels independent of ACTH levels, indicating a direct stimulating effect of orexin on the adrenal cortex.<sup>[19]</sup> But, in spite of these findings, Patel *et al.*'s study confirmed insignificant effect of orexin antagonists on

ACTH and cortisol serum levels as well as on the markers of sympathetic nervous system.<sup>[20]</sup>

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.<sup>[21,22]</sup>

Many studies showed that the body metabolism, mainly glucose is regulated by central orexin through regulation of hepatic glucose production, skeletal glucose consumption, and thermogenesis. High orexin or dys-rhythmic in orexin secretion is linked with the development of obesity and insulin resistance.<sup>[23,24]</sup> 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.<sup>[25]</sup>

Tsuneki *et al.*'s 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.<sup>[26]</sup>

Flores *et al.*'s 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.<sup>[27]</sup>

## Role of Orexin in Psychiatric Disorders

### Depression

Among important etiological factors involved in the pathophysiology of depression, disturbances of monoamines and HPA are the main mechanistic pathways leading to functional disorders of neuroplasticity, which is regarded as a cardinal step in the onset of depression.<sup>[28]</sup>

It has been reported that orexin level is significantly decreased in patients with depression in comparison with healthy subjects.<sup>[29]</sup> But, paradoxical high orexin serum levels are seen in some depressed patients, which

normalized by selective serotonin reuptake inhibitors. Since, orexin-A cerebrospinal fluid (CSF) levels negatively correlated with depressive symptoms.<sup>[30]</sup>

Long-term antidepressant agents improve orexin serum levels regardless the type of anti-depressant medications.<sup>[31]</sup> 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 responsible for modulation of orexinergic activity.<sup>[32]</sup> 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.<sup>[33]</sup>

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 messenger RNA (mRNA) expression and orexin-A were reduced compared with control.<sup>[34]</sup>

Previous preclinical study revealed a strong connection between low orexin and risk of depression which are inconsistency with previous studies that illustrated hypo-activity of orexinergic neurons in patients with depression, since short-term anti-depressant therapy improves sleep pattern through increasing and decreasing the expression of mRNA of orexin-A and orexin-B respectively.<sup>[35]</sup>

Ito *et al.* showed that administration of orexin-A leads to significant reduction of despair behavior in depression with important hippocampal neurogenesis via up-regulation of neuropeptide Y. These changes are inhibited by co-administration of orexin-A antagonist.<sup>[36]</sup>

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.<sup>[17]</sup> 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 VP and prevents depressive behavior. Therefore, high orexin in 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.<sup>[37]</sup>

### Schizophrenia

The association between orexin and schizophrenia had not previously explored precisely.<sup>[38]</sup> Clinical and preclinical findings proposed that orexin and orexin agonist are of great value and useful in

treating cognitive deficit in schizophrenia.<sup>[39]</sup> There are widespread connection and interaction between orexin and dopaminergic neurons in midbrain, thalamo-cortical and amygdala suggesting the potential role of orexinergic neurons in schizophrenia.<sup>[40]</sup>

Modafinil is an atypical dopamine reuptake inhibitor used in the treatment of narcolepsy and anti-psychotic drug-induced sleep disorder [Figure 3].<sup>[41]</sup> Modafinil has been revealed as a complement of drugs in therapy of schizophrenia; it reduced negative symptoms with no effect on the positive symptoms. Modafinil improves locomotors and psychomotor performances through activation of orexinergic neurons.<sup>[42]</sup>

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.<sup>[43]</sup> As well, dopamine antagonists that cause weight gain lead to activation of orexin pathway, but; dopamine antagonists, which not cause weight gain not activate orexin pathway.<sup>[44]</sup> Nevertheless, amphetamine which indirectly activates dopamine leads to activation of orexinergic neurotransmission despite of induction of weight loss. Moreover, clozapine activates only orexinergic neurons in prefrontal cortex.<sup>[45]</sup> 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.<sup>[46]</sup> As well, Chen *et al.* illustrated that orexin-A is stimulated and upregulated by nonobese genic antipsychotic drugs.<sup>[47]</sup> 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.<sup>[48]</sup> Furthermore, orexin agonist like modafinil ameliorates cognitive function, attention, and antipsychotic-induced sedation.

### Addiction

Orexinergic system has broad projections and connections to different brain area which are concerned with

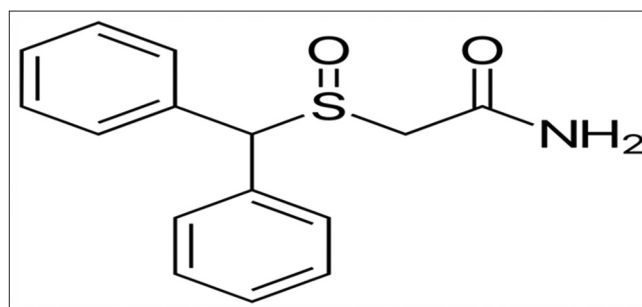


Figure 3: Chemical structure of modafinil

drug-induced neuroadaptation, including midbrain dopaminergic neurons, ventral tegmental area (VTA), nucleus accumbens (NA), amygdale and mPFC. Drug abuse leads to augmentation of dopaminergic activity in NA through activation of orexinergic neurons at mesocorticolimbic pathway.<sup>[49]</sup> Correspondingly, experimental studies illustrated that OX1R and OX2R are highly expressed in the NA leading to inhibitory effect instead of excitatory effects seen on VTA, amygdale and mPFC. Therefore, a differential effect of orexin is receptor type dependent.<sup>[50]</sup>

Acute administration of methamphetamine, nicotine and amphetamine leads to activation of orexinergic neurons at lateral hypothalamus. However, acute administration of cocaine and morphine not affect orexinergic neurons. Besides, chronic administration of abusing drugs causing activation of orexinergic neurons mainly at OX2R receptors, but; chronic rising dose of abusing drugs leads to down-regulation of orexinergic receptors.<sup>[51]</sup> Carr and Kalivas reported that orexin is an important mediator enables the cocaine to induce addiction-like behavior in rats due to dopaminergic neuronal changes.<sup>[52]</sup> As well, James *et al.* verified that orexinergic neurons at lateral hypothalamus play a vital role in expression of addiction-like phenotype.<sup>[53]</sup> Thus, 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 and the phase of abstinence, since it increased during addiction phase and reduced during the withdrawal phase. This reduction leads to increased in the craving and risk of relapse.<sup>[54]</sup> Therefore; orexin serum level is regarded as potential biomarker predicts time and risk of smoking relapse.

Tsai and Huang reported that the orexin serum level is increased in heroin addicts shifted on methadone maintenance therapy compared with controls suggesting that methadone increases orexin serum levels.<sup>[55]</sup> 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.<sup>[56]</sup>

### Sleep disorders

Narcolepsy is an excessive daytime sleepiness or an intractable urge to sleep in, which duration of rapid eye movement sleeps (REM) is reduced. Cataplexy is a sudden reduction in muscle tones with preserved consciousness. Narcolepsy is commonly associated with cataplexy, which triggers by emotional stimuli.<sup>[57]</sup> Methylphenidate, modafinil and other psychostimulants

are effective in the management of these sleep disorders.<sup>[58]</sup> Dysregulation of NREM sleep leads to narcolepsy only, whereas; Dys-regulation of REM sleep leads combined narcolepsy with cataplexy.<sup>[59]</sup> It has been reported that orexin increases vigilance through increases awaking time and decreases 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). As well, orexin activates cholinergic neurons in basal forebrain, which also important for arousal statuses.<sup>[60]</sup> Yamanaka *et al.*'s study illustrated that activation of OX2R by orexin leads wakefulness which is mediated by histamine neurotransmitter, since antihistamine blocks the excitatory effect of orexin. While, activation of OX1R by orexin leads wakefulness, which is mediated by noradrenalin neurotransmitter.<sup>[61]</sup> 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.<sup>[62]</sup> Therefore, these findings unveil that orexin is an important neuropeptide in the regulation of sleep and consolidated wakefulness, Figure 4.

## Role of Orexin in Neurodegenerative Diseases

### Parkinson disease

Orexinergic neurons are severely affected in PD; previously Fronczek *et al.* confirmed that orexinergic neurons density was reduced in the prefrontal cortex by 40% with significant reduction in CSF orexin levels in PD patients compared to the healthy control.<sup>[63]</sup>

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

Moreover, orexin A improves dopaminergic neurons in PD through attenuation the reduction of tyrosine hydroxylase and activation of brain derived neurotrophic factor (BDNF) in the substantia nigra.<sup>[44]</sup> Therefore,

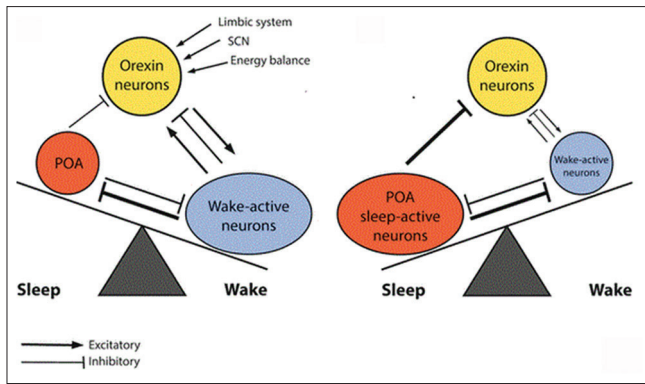


Figure 4: Role of orexin in sleep disorders

orexin antagonist may increase risk of PD due to reduce the neuroprotective and stimulating effects on the dopaminergic neurons at substantia nigra.<sup>[67]</sup> Sheng *et al.* found that orexin play 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 BDNF in dopaminergic neurons of the substantia nigra. The upregulation of BDNF is mainly via OX1R.<sup>[68]</sup> 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.<sup>[69]</sup>

### Alzheimer disease

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

Dementia with Lewy bodies characterized by an elevation in  $\alpha$ -synuclein level, which accumulated in the orexin containing neurons at 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.<sup>[74]</sup> Therefore, there are complexities in the orexinergic system according to the clinical presentation and sleep pattern in patients with AD.

### Huntington's disease

Huntington's disease (HD) is a hereditary neurodegenerative disorder characterized by personality changes, motor disturbances, cognitive decline and weight loss.<sup>[75]</sup> 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.<sup>[76]</sup> In HD, there are neurodegeneration involving neostriatum and cerebral cortex, with the manifestation of intra-neuronal 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 B are synthesized from the same precursor gene and are expressed in the same neurons with their cell bodies concentrated to the lateral hypothalamus.<sup>[77]</sup> 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 pg/ml but in HD and narcolepsy this level is decreased below 110 pg/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.<sup>[78,79]</sup> However, Meier *et al.* illustrated that CSF and serum orexin levels are of no diagnostic value in prediction and follow up of HD.<sup>[80]</sup>

Cabanas *et al.* observed that orexin in HD has aberrant effect leads to abnormal sleep pattern, and thus orexin antagonist suvorexant may be of great value in restoring normal sleep and behavioral disturbance in HD.<sup>[81]</sup> In addition, despite reduction of orexinergic density in HD, 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.<sup>[81,82]</sup>

### Multiple sclerosis

Multiple sclerosis (MS) is a demyelinating disease 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.<sup>[83,84]</sup>

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.<sup>[85]</sup>

Considering the multiplicity of symptoms associated with MS, there is possibility that hypocretin system function might be involved in the pathogenesis of the disease. Papuč *et al.* showed that orexin CSF level did not 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.<sup>[86]</sup> 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 implicated in the pathogenesis of hypersomnia and cognitive deficit in patients with MS.<sup>[87]</sup> Recently, Pallais *et al.* confirmed that orexin has a neuroprotective effect in MS through inhibition of inflammatory and proinflammatory mediators mainly matrixmetaloproteinase (MMP-3, MMP-9) which are involved in damage of neuronal matrix proteins. Consequently, low CSF orexin level indicate underlying active disease.<sup>[88]</sup>

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

### Amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis (ALS), also known as motor neuron disease 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. 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.<sup>[89]</sup> 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.<sup>[90]</sup> Moreover, the pathogenesis of ALS is associated of lateral hypothalamic lesions, a site of orexinergic system leading to sleep disturbances and hypersomnia.<sup>[91]</sup>

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

### Orexin antagonists and neurobiology

Regarding orexin antagonists, suvorexant is a dual orexin receptor antagonist was approved by Food and Drug Administration on 13 August 2014.<sup>[92]</sup> Other orexin antagonists are almorexant, lemborexant and filorexant, which 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.<sup>[93]</sup>

Suvorexant [Figure 5] is the first orexin antagonists approved in the United State for treatment of insomnia, which is effective in reduction time to sleep onset and increasing of total sleeping time.<sup>[94]</sup> 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.<sup>[95]</sup>

Hatta *et al.*'s 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 regulation of circadian biology.<sup>[96]</sup> Delirium is proposed to be related 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.<sup>[97]</sup> Therefore, orexin receptor antagonists may play important role in the regulation of hypothalamic and

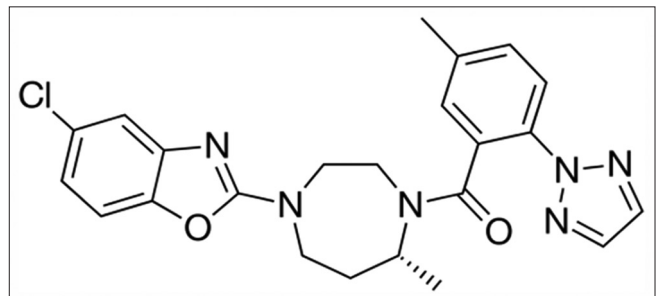


Figure 5: Chemical structure of suvorexant

brain stem stress during acute injury. Moreover, a recent study by Kawada *et al.*'s study illustrated that suvorexant add on therapy to ralmeton in the management of sleep disorders in patients with acute stroke is more effective than when combined with benzodiazepines.<sup>[98]</sup>

It has been verified that prolong alcohol consumption is associated with sleep disturbance which is a powerful factor for relapse and set-back to alcohol use. Suvorexant reduces the motivation properties of alcohol so; it plays a crucial role in the prevention of alcoholism.<sup>[99]</sup>

Gentile *et al.*'s study revealed the possible role of suvorexant in reduction of motor impulsivity of cocaine-induced psycho-stimulant effects. Thus, suvorexant may be effective in attenuation of cocaine withdrawal syndrome.<sup>[100]</sup>

As well, suvorexant had placebo like effect on EEG in comparison with zolpidem which has a significant reduction in the spectral density of REM and non-REM sleep pattern.<sup>[101]</sup>

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.*'s study.<sup>[102]</sup>

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.<sup>[103]</sup> Orexin A is implicated in the pathogenesis of obesity; it promotes hyperphagia through central activation of cannabinoid receptors and inhibition of melanocyte stimulating hormone.<sup>[104]</sup> Both orexin-A and endocannabinoid increases glucose response of neuronal excitability in arcuate nucleus leading to induction of feeding and obesity.<sup>[105]</sup>

Therefore, 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 psycho-neurological 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. As well, ratio of orexin serum level: CSF orexin level may reflect the activity of endogenous orexinergic system.

## Conclusion

Orexinergic system is involved in the different psychiatric and neurological disorders, therefore targeting of this system could be 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.

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## Conflicts of interest

There are no conflicts of interest.

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