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Review article

Sex-dimorphic functions of orexin in neuropsychiatric disorders

Jinghan Zhang [a,1], Kangyu Jin [a,b,1], Bing Chen [a,b], Shangping Cheng [a,b], Jinfan Jin [c], Xiaolan Yang [c], Jing Lu [a,b,*], Qinghai Song [c,**]

[a] Department of Psychiatry, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, 310003, China
[b] The Key Laboratory of Mental Disorder Management in Zhejiang Province, Hangzhou, 310003, China
[c] Department of Psychiatry, Lishui Second People's Hospital, Lishui, Zhejiang, 323000, China

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ABSTRACT

The orexin system regulates a variety of physiological functions, including the sleep-wake cycle, addiction, foraging behavior, stress and cognitive functioning. Orexin levels in central and peripheral are related to the pathogenesis of many diseases, most notably the narcolepsy, eating disorders, stress-related psychiatric disorders, and neurodegenerative diseases. Recently, it has been reported that the orexin system is distinctly sexually dimorphic, and is strongly associated with neuropsychiatric disorders. In this review, we analyzed advancements in the sex differences in the orexin system and their connection to psychoneurological conditions. Considering the scarcity of research in this domain, more research is imperative to reveal the underlying mechanisms.

1. Introduction

The orexin system in the lateral hypothalamus regulates a wide variety of biological functions, most notably the sleep-wake cycle [1,2], foraging behavior [3,4], stress cognitive functioning [5], and drug addiction [6].

Orexin(ORX, or hypocretin)-A(1) and ORX-B(2) are neuropeptides that were discovered concurrently by two research groups in 1998 [7,8]. The orexins were named by Sakurai [8] et al. (1998) after the Greek word orexis, which refers to appetite. Conversely, De Lecea et al.(1998) named this newly discovered peptide hypocretin [7]. However, for the sake of convenience and clarity in nomenclature, this molecule shall be referred to as "orexin" throughout the subsequent text. Orexins, cleaved from the single precursor peptide prepro-orexin (prepro-Hcrt or prepro-ORX), exhibit widespread projections within the perifornical/lateral hypothalamus,

Abbreviations: OXR, orexin; PVN, hypothalamus paraventricular nucleus; OXR, orexin receptor; LH, luteinizing hormone; CRH, corticotropin-releasing hormone; mRNA, messenger Ribonucleic Acid; ACTH, stimulating adrenocorticotropic hormone; HPA axis, hypothalamic-pituitary-adrenal axis; GR, glucocorticoid receptors; CSF, ventricular cerebrospinal fluid; SCZ, Schizophrenia; AD, Alzheimer's disease; DMH, dorsomedial hypothalamus; PFA, perifornical area; VTA, ventral tegmental area; GnRH, gonadotropin releasing hormone; ACTH, adrenocorticotropic hormone; REM, rapid eye movement sleep; pCREB, phosphorylated cyclic adenosine monophosphate response element-binding protein; DREADDs, Designer Receptors Exclusively Activated by Designer Drugs; ASST, attentional set shifting task; HD, Huntington's disease; NREM, natural non-rapid eye movement; BDNF, brain-derived neurotrophic factor.

* Corresponding author. Department of Psychiatry, The First Affiliated Hospital, Zhejiang University School of Medicine; the Key Laboratory of Mental Disorder's Management of Zhejiang Province, Hangzhou, 310003, China.
** Corresponding author. Department of Psychiatry, Lishui Second People's Hospital, Lishui, Zhejiang, 323000, China.
E-mail addresses: lujing2016@zju.edu.cn (J. Lu), qinghai_song@126.com (Q. Song).
[1] The authors contribute equally to this work.

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thalamus, and brainstem [7]. Sakurai et al. (1998) identified two G protein-coupled receptors and their natural ligands, which contribute to innervating food consumption and are upregulated in response to fasting [8]. Orexinergic neurons are primarily located in the lateral hypothalamus adjacent to the fornix, perifornical area (PFA) and dorsomedial hypothalamus (DMH). These neurons project to multiple brain regions to perform their physiological functions. Among them, the ventral tegmental area (VTA) is an pivotal projection target. In this region, fiber terminals of orexin neurons are adjacent to the neuronal cell bodies and dendrites of the VTA. Additionally, orexinergic neurons may project to other brain regions associated with feeding and sleep mechanisms, such as the amygdala and nucleus accumbens. Expression of orexin receptors is primarily observed in multiple brain regions relevant to orexin function. Specifically, the orexin receptor 1 (OX_1R) is primarily expressed in the prefrontal and subcortical regions, paraventricular nucleus of the thalamus, locus coeruleus and hippocampus. By contrast, the orexin receptor 2 (OX_2R) is primarily expressed in the lateral hypothalamus, cerebral cortex, hippocampus, hypothalamic nuclei, and septal nucleus [9–11]. Orexinergic peptides are involved in many physiological functions and disorders [12]. This review examines the advancements in the sex-dependent role of orexin and its relevance to neuropsychiatric disorders, and intends to explain its potential mechanism.

2. The physiological role of orexin in neuropsychiatric disorders

Alterations of central and peripheral orexin levels are connected with conditions such as narcolepsy, eating disorders, stress-related psychiatric disorders, social interaction, and neurodegenerative disease [4,13–15]. ORX deficiency can lead to a narcoleptic phenotype with sleepiness, sleep instability, and cataplexy, indicating a crucial role for ORXs in the regulation of sleep-wake states [16]. Although ORX-A injection induces daytime feeding, it does not influence overall food consumption or body weight gain [17]. In addition, it plays a role in reward-seeking mechanisms and drug addiction [6,18]. Not only does ORX-A secretion increase related to the wakefulness–sleep cycle, but also maximally during social interaction, and anger, thus regulating complex human behaviors [19,20]. The orexin system serves as a vital regulator of numerous physiological functions, including autonomic control [21], thermoregulation [22], and energy homeostasis [23]. Additionally, orexin is also significant in stress responses [24]. Acute stress stimulates orexinergic neurons, which reciprocally affect acute stress-induced behavioral responses [25–28]. In studies examining the impacts of repeated exposure to prototypical restraint stress, hypoactivity and hyperactivity within the orexin system were reported [27,29]. Decreased orexin levels are closely related to sleep disorders in patients with Alzheimer's disease (AD), with research showing that a reduction in orexin may lead to neuronal damage and decreased synaptic connections, thus exacerbating cognitive dysfunction, in patients with AD [30].

3. The sex differences of the orexin system in preclinical studies

The expression of orexin and its receptors is associated with sexual dimorphism during growth and development. Prepro-orexin mRNA levels in the hypothalamus of adult female rats were found to be higher than those in males [31] (Table 1). The number of orexinergic neurons in the lateral hypothalamus is higher in proestrus female rats than in male rats [32]. In addition, the expression levels of ORX-1 receptor mRNA in the pituitary gland and ORX-2 receptor mRNA in the adrenal gland are significantly higher in male than in female rats [33]. Loewen et al.(2017) found that OX_2R expression was higher in the hypothalamic paraventricular nucleus (PVN) in female rats than in male rats [34]. A thorough analysis of the distribution of orexin A showed that sex differences were noticeable in the lateral and posterior hypothalamus [35]. In addition, its expression is regulated by fasting [36] and the reproductive system [31].

Reproductive hormones regulate orexin concentration. Orexin levels and expression of the OX_1R protein in the hypothalamus are the highest during pre-estrus,. This is attributed to a surge in progesterone and estradiol, which are both reproductive hormones that regulate the concentration of orexin [37,38]. According to Deurveilher et al.(2008), it was also discovered that estradiol enhances the c-Fos expression of in hypothalamic orexin neurons that contain [39]. Conversely, in the hypothalamus of ovariectomized female rats, the expression of OX_1R decreased, while estradiol replacement reinstated orexin expression to elevated levels in normal circulating rats [38,40]. Reciprocally, the orexin system affects sex-hormone production. In female rats that have undergone ovulation suppression, orexin increases the release of luteinizing hormones (LH) only when they have been previously primed with estrogen and progesterone [11]. Recently, Martyńska et al.(2021) proved that orexin-A exerted a downregulatory effect on the synthesis and release of luteinizing hormones in immature female rats [41]. Androgens also regulate orexin levels. Gonadectomy reduced OX_1R expression in the anterior hypothalamus in male rats, which could be restored by both testosterone and dihydrotestosterone [40]. However, no correlation was observed between testosterone concentrations and activated orexin neurons in male rats.

The distribution of orexin immunoreactive fibers exhibits an overlap with the gonadotropin-releasing hormone (GnRH) system in the arcuate nucleus-median eminence regions and the septo-preoptic area, indicating that orexin influences the secretion of pituitary LH by regulating GnRH release [42,43]. Soejima et al. (2022) reported that orexin modulated the gonadotropin-releasing hormone (GnRH) expression, resulting in enhancing gonadotropin levels in a dose-dependent manner [44]. Additionally, orexin interacts with the pituitary bone morphogenetic protein system to regulate gonadotropin expression by modulating clock gene expression [44]. Because orexin alters the pulses of GnRH release, it plays a pivotal role in regulating LH secretion in the anterior pituitary gland, which may affect testicular function by regulating steroidogenesis in male Leydig cells [45,46]. The presence of sex steroids, particularly ovarian sex hormones, is linked to increased activity of orexin neurons. This suggests that ovarian hormones may strengthen the ability of orexin to influence complex behaviors, including arousal, sleep, stress, and feeding [47].

Furthermore, Bonnavion et al.(2015) reported that orexin triggered an increase in the expression of corticotropin-releasing hormone (CRH) neurons in PVN by OX_2R activation [48]. Additionally, Lu et al.(2017) found a significant positive correlation between the

prepro-orexin and mRNA levels of CRH and in the hypothalamus of female, but not male, chronically unpredictable mild-stress rats [49]. In addition to stimulating adrenocorticotropic hormone (ACTH) and corticosterone via CRH, orexins may directly promote ACTH release through their action on pituitary OX_1R and OX_2R [50]. Thus, we concluded that the role of sex differences in orexin is dependent on the hypothalamic-pituitary-adrenal axis (HPA axis).

Impaired habituation of the HPA axis accounts for impaired reversal learning scores in female rats under repeated restraint stress compared with male ones, which can be reversed by the chemogenetic inhibition of hypothalamic orexin neurons [5]. Due, in part, to the glucocorticoid receptor (GR) action of the prepro-orexin promoter, the elevated activation of orexin neurons in female rats accounts for their inability to adapt to repeated stress [5]. The HPA axis seems prominent in orexin-mediated sexually dimorphic behavioral and neuroendocrine adaptations. In addition, orexin directly regulates reproductive function in male and female animals in a sex-dependent manner. However, the sexual dimorphism of orexin in regulating steady-state function and complex behavior in animals is not completely clear, as most studies utilized male animals as subjects.

4. Sex differences of the orexin system in neuropsychiatric diseases

Considering that neuropsychiatric diseases generally show significant sex differences [51,52], it is important to study the role of orexins in neuropsychiatric disorders. Given that most prior studies on orexins have been conducted on male animals, we mainly discuss articles including both female and male animals to discuss the advances in sex differences in the orexin system.

4.1. Sleep disturbance

During the reproductive lifespan, the prevalence of sleep disturbance was found to be significantly higher in women than in men. Epidemiological evidence suggests that women are more susceptible to sleep issues during hormonal transitions such as puberty and menopause. Nevertheless, the specific role of orexin in mediating these sleep problems remains elusive [53,54].

Narcolepsy is a rare brain disease caused by the selective deficiency or impairment of orexin neurons in the lateral hypothalamus. Orexin neuron deficiency disinhibits rapid eye movement sleep (REM) during active period, triggering episodes of paralysis and cataplexy during wakefulness [55,56]. Ingravallo et al. (2024) reported that female patients showed a greater narcolepsy-related burden and more severe sleepiness than male ones [57]. Notably, researchers have examined the variance in plasma and cerebrospinal fluid (CSF) orexin levels between the sexes in narcolepsy. Multiple linear regression analyses revealed that the sleep latency was significantly linked to their CSF orexin levels and sex in patients with narcolepsy [58,59]. Zhu et al. (2020) found a significant reduction in plasma orexin concentrations in patients with narcolepsy, compared with healthy individuals [60]. However, they found no significant correlations between sex and electrophysiological indicators [60](Table 2). Barateau et al.(2019) discovered that clinical autonomic dysfunction resulting from narcolepsy was not linked to plasma orexin levels, and did not show any sex differences [61]. Albeit the inadequate investigation of sexual dimorphism in narcolepsy, recent studies on orexin-deficient mice have revealed sex-specific differences in cataplexy. For example, some researchers have reported that female orexin-deficient mice exhibit a higher incidence of cataplexy than male mice [62–64]. Similarly, Fujiki et al. (2006) reported a significantly higher prevalence of obesity in female orexin-deficient narcoleptic mouse models. This phenomenon has been linked to elevated serum leptin levels, indicating a partial mechanism for leptin resistance [65].

In summary, clinical studies in patients with narcolepsy have shown that lower CSF and serum orexin levels are significantly associated with the onset of narcolepsy. Some researchers have further reported no sex differences in orexin levels in narcolepsy models. This may be due to the low levels that were often subject to detection errors and the small sample sizes collected. Furthermore, the traditional detection method for orexin levels is easily affected by the conversion and degradation of prepro orexin and orexin;

Table 1
Preclinical studies on sex differences of the orexin system Based on preclinical studies, here is a summary of the differences in orexin levels between males and females. The summary includes information about the specific information of orexin measurement, and whether females showed higher levels than males. Each study is also cited for reference.

Orexinergic system		Sampling site	Intervention	Sex difference	Citation
Prepro-orexin mRNA		Brain	No	Higher in female rats (than males)	Grafe et al. (2017) [5]
		Hypothalamus	Fasting	No significance	Iwasa et al. (2015) [36]
Orexin A		Hypothalamus	No	Higher in female rats	Taheri et al. (1999) [35]
		CSF	Restraint stress	Higher in female rats	Grafe et al. (2017) [5]
The number of orexinergic neurons		Lateral hypothalamus	No	Higher in female rats	Andrew et al. (2022) [32]
				Higher in female rats	Grafe et al. (2017) [5]
			High-fat diet	Higher in female mice	Pirnik et al. (2008) [70]
			High-fat diet	Higher in female rats	Freeman et al.(2021) [79]
			Fasting and satiety	No significance	Buczek et al. (2020) [74]
			Fasting	Higher activated neurons in female rats	Funabashi et al. (2009) [71]
OXR mRNA	OX_1R	Pituitary gland	No	Higher in male rats	Johren et al. (2001) [33]
		Frontal cortex	Chronic stress	Higher in female rats	Lu et al.(2017) [49]
	OX_2R	Adrenal gland	No	Higher in male rats	Johren et al. (2001) [33]
		Hypothalamus	No	Higher in female rats	Loewen et al. (2017) [34]
	Both	Nucleus accumbens	No	Higher in female rats	Daiwile et al. (2019) [124]

Table 2
Clinical studies on sex differences of the orexin system. Based on clinical studies, here is a summary of the differences in orexin levels between male and female patients. The summary includes information about the specific information of orexin measurement, and whether females showed higher levels than males. Each study is also cited for reference.

Group	Detection index	Sex difference	Citation
Healthy control	Plasma level of orexin A	Higher in females(than males)	Lu et al. (2021) [94]
Narcolepsy patients	Plasma level of orexin A	No significance	Zhu et al. (2020) [60]
Depression patients	Hypothalamus concentration of orexin A	Higher in female.	Lu et al. (2017) [49]
AD patients	CSF level of orexin A	Higher in female.	Schmidt et al. (2013) [101]
		No significance	Dauvilliers et al. (2014) [99]
SCZ patients	Plasma level of orexin A	No significance	Lu et al. (2021) [94]

thus, a more accurate and effective detection method should be selected. Hopkins et al.(2021) developed a validated LC-ESI-MRM assay for absolute quantification of orexin A in the CSF of individual mice. This methodology is anticipated to expedite research endeavors on sleep- or arousal-associated brain disorders in relevant rodent models [66]. The correlation between narcolepsy and reduced orexin expression is unequivocal and potentially influences sleep latency, body weight, and occurrence of cataplexy. However, studies on sex differences in this connection are scarce, indicating the need for further research to validate these findings.

4.2. Eating disorders

Past studies have shown sex-related differences in the orexin neurons in the lateral hypothalamus, which are pivotal in regulating feeding behavior. These sex-specific disparities could potentially be attributed to the influence of gonadal steroid hormones, which are known to induce variations in feeding behavior, as evidenced by the increased food intake observed in ovariectomized females and the decreased intake in orchiectomized males [67]. Orexin-A-induced food intake was suppressed by treatment with a selective OX_1R antagonist [68]. By comprehending the neural foundation of sex-based distinctions in eating habits, we can better understand disorders relating to sexes [69], such as eating disorders. However, clinical studies on the relationship between orexin levels and feeding behavior is limited, and most existing studies have been conducted in animals.

Pirnik et al.(2008) found that female mice experienced a notable increase in orexin neuron activation following exposure to a high-fat diet, whereas male mice did not exhibit any significant changes [70]. Moreover, some researchers found that fasting increases the number of orexin neurons with phosphorylated cyclic adenosine monophosphate response element-binding protein (pCREB) in female rats, but not in male rats [71,72]. Another study revealed that fasting did not influence the expression of hypothalamic prepro-ORX mRNA in either sex [36]. However, this led to a notable increase in OX_1R mRNA levels in prepubertal female rats [36]. Notably, OX_1R plays a pivotal role in the response of female rats to sucrose rewards, as well as in their tendency to seek sucrose cues for reinstatement [73]. Buczek et al.(2020) showed that the tendency of females to have a stronger desire to eat than males is linked to the function of the OX_1R receptor. However, no sex-related differences were observed [74]. Additionally, Tsuneki et al. (2008) exhibited that orexin deficiency contributed to age-associated declines in glucose tolerance and insulin resistance in non-obese male mice, whereas female mice displayed modest obesity under a standard chow diet. Additionally, upon a high-fat diet regimen, female orexin-knockout mice exhibited more profound abnormalities, culminating in severe obesity [75]. These outcomes underscore the crucial functions of orexins in regulating insulin sensitivity in glucose metabolism. Ramanathan et al.(2014) found that female orexin-knockout mice showed higher body weights and serum leptin levels than wild-type mice, but there was no sex differences between them [76].

Furthermore, orexin has been implicated in binge eating [77,78]. Freeman et al.(2021) discovered that female rats showed a higher consumption of palatable foods than males at a low cost (normalized to body weight), whereas no significant differences were observed at higher prices. They also observed more expressions of orexin neurons and Fos expression (a measure of recent nerve activation) in female than in male rats [79]. Additionally, Faesel et al.(2023) found that female mice exhibited a greater binge-eating response to an intermittent Western diet than males, although orexin deficiency had no impact on this behavior. Notably, female orexin-deficient mice typically exhibited a higher body weight and displayed augmented hypophagia as well as elevated stress levels subsequent to binge eating, compared with their wild-type counterparts [80].

In summary, the findings in this field of research are consistent; both when fasting when fed a high-fat diet, female mice had a significant increase in orexin expression in the hypothalamic regions compared with males, which may be due to the role of orexin in increasing appetite and promoting feeding; however, this promotion persists after satiation. This appears to be similar to the pathogenesis of binge-like eating episodes [80]; however, it is difficult draw conclusions without more relevant studies.

4.3. Stress and cognitive flexibility

Psychiatric disorders linked to stress are reported to be twice as prevalent in women, yet the exact neurobiological factors contributing to these sex differences remains unclear [51,52]. Grafe et al.(2017) found that orexin expression is stimulated in female rats after restraint stress [5]. The higher prevalence of the glucocorticoid receptor on the orexin promoter in females than in males underlies the inability of female rats to habituate to repeated stress [5]. Moreover, the inhibition of orexin receptors by Designer Receptors Exclusively Activated by Designer Drugs (DREADDs) through repeated restraint eliminated the enhanced hypothalamic-pituitary-adrenal response in female rats. According to Grafe et al.(2017), females who experience restraint stress show impaired reversal learning due to a lack of habituation in HPA axis development [5]. When chemogenomic inhibition was used to

target female hypothalamic orexin neurons in the lateral hypothalamus during stress exposure, the resulting neuroendocrine and behavioral outcomes were similar to those observed in males. Grafe et al. (2019) conducted a further investigation into the morphological characteristics of putative orexin neurons in adult male and female rats, discovering that putative orexinergic neurons in female rats had higher dendritic morphology and spine densities in the basal state, resulting in increased excitatory inputs to orexin neurons, and a more significant number of mushroom spines. This may explain why female rats are more sensitive to stress [81]. Furthermore, exposure to stress led to a notable decrease in the dendritic length, number of nodes, and branching complexity in orexin neurons. Notably, Gargiulo et al.(2021) reported that repeated stress consistently increased the awakening time in female rats, whereas the effects of stress on males were more short-lived [82].

Recently, orexin was believed to play a sex-dependent role in cognitive function. Durairaja et al.(2021) found that orexin deficiency selectively impairs the intradimensional shift phase of the attentional set-shifting task (ASST) in female orexin-deficient mice, while selectively improving the first reversal learning phase in male ones [83]. Additionally, Durairaja et al. (2022) reported that the administration of the selective OX_1R antagonist SB-334867 impaired the first and second reversal stages of the ASST in female mice, but had no effect in male mice [84]. These results highlight the sex differences of orexin in regulating stress and cognitive flexibility, emphasizing the necessity for further research in this field.

4.4. Depression

It is widely understood that the orexin system plays a crucial role in regulating various neurophysiological and behavioral processes, including sleep/wake cycles [85,86], food intake [77,87], stress and cognitive flexibility [5,83], drug addiction [6] and monoaminergic neurotransmission [88,89], which are commonly disrupted in individuals with depression. Both clinical and preclinical studies of the orexin system have previously demonstrated sexual dimorphism in depression.

Lu et al. (2017) found that orexin A immunoreactivity was significantly higher in female than in male postmortem human brains, indicating the significant role of orexin in the etiology of depression [49]. The study further revealed that male patients with depression who had succumbed to suicide exhibited significantly elevated levels of OX2R mRNA expression in the anterior cingulate cortex, in comparison to sex-matched control subjects. In addition, the study found a significant positive correlation between hypothalamic prepro-orexin-mRNA and CRH mRNA, accompanied by a marked increase in orexin-receptor-1-mRNA expression in the frontal cortex of female rats subjected to chronic, unpredictable mild stress [49]. Winsky-Sommerer et al.(2004) further reported that corticotropin-releasing factors stimulate the release of hypocretins after stressor stimuli [90].

Based on the above research, it is clear that the orexin system exhibits significant sex-dimorphic functions in depression, possibly by interacting with the HPA axis. However, further investigations are imperative to elucidate how orexin influences the pathogenesis of depression and its relationship with the related clinical manifestations.

4.5. Schizophrenia

Patients with schizophrenia (SCZ) experience impaired physiological functions in the sleep-wake cycle, in addition to impairments in attention, cognition, and energy balance, which are all regulated by the orexin system [91]. It is worth noting that SCZ displays sex differences in its disease process, with males experiencing an earlier onset of the first episode than females. Additionally, the gene expression and clinical manifestations of SCZ vary depending on sex [92,93]. Therefore, the potential sex differences in the orexin system in this disease merit attention. Lu et al.(2021) found that central orexin neurotransmission declined in patients with SCZ, particularly in female patients, which was reflected in the plasma [94]. Notably, orexin A levels were increased in patients with SCZ receiving different antipsychotic treatments (incl. clozapine),while this increase was most prominent in those patients taking less obesogenic antipsychotics [95]. Some studies have also indicated that antipsychotic medication may decrease plasma orexin A levels [96,97]. Hence, future clinical studies should incorporate psychiatric medications as factors influencing orexin levels. Presently, there is no conclusive evidence suggesting sex differences between male and female patients with SCZ and further clinical and preclinical studies are required.

4.6. Neurodegenerative disease

Extensive research has demonstrated a correlation between orexin levels and the pathogenesis of neurodegenerative disorders, including AD, Parkinson's disease (PD), Huntington's disease (HD). For example, during natural non-rapid eye movement (NREM) sleep, orexin levels decline, leading to the expansion of the extracellular space in the brain, and subsequently enhancing the clearance of beta-amyloid and tau proteins from the interstitial space [98]. In a postmortem analysis, a decrease in the number of orexin neurons within the hypothalamus and a reduced concentration of orexin in the ventricular cerebrospinal fluid (CSF) were observed in patients with AD compared with the control group [98]. However, other researchers reported that orexin-A CSF levels in patients with AD were higher than those in the control group [99,100], which may be associated with sleep deterioration and neurodegeneration. Interestingly, Schmidt et al.(2013) found that the number of immunoreactive neurons in the postmortem hypothalamus and ventricular CSF-orexin-A levels were reduced in patients with AD. The levels of orexin-A in the CSF exhibited sex dependency, with females showing higher levels than males [101]. However, Dauvilliers et al. (2014) found no sex differences in CSF orexin levels in patients [99]. Unfortunately, there is a lack of pertinent research to support these conclusions. Notably, Wennström et al. (2012) revealed sex-dependent alterations in CSF orexin levels in patients with AD or dementia with Lewy bodies [102]. MK-1064, a selective OX_2R antagonist, decreased wakefulness and increased both NREM sleep and total sleep time in both sexes in transgenic tauopathy mouse

models [103,104]. MK-1064 further normalizes the hyperarousal phenotype in male mice, whereas the response is more transient in female mice [103,104].

Researchers have additionally reported a decrease in the number of orexinergic neurons in the lateral hypothalamus area in PD animal models [105,106]. However, published results regarding the plasma and CSF orexin levels in PD animal models have been inconsistent [107–110]. This may be partially attributed to differences in the pre-analysis and analytical methods used in the different studies. However, no studies have reported sex-based differences in orexin levels in patients with PD. We believe that more high-quality studies are required in the future. These studies should also include patients of different ages, sexes, and PD stages.

Studies have shown that patients on HD have a reduced number of orexinergic neurons [111]. Nevertheless, there were no significant variations in cerebrospinal fluid orexin levels in patients undergoing hemodialysis [112]. In a mouse model of HD, a significant decrease in the number of orexinergic neurons and cerebrospinal fluid orexin levels was observed [113]. Recently, Cabanas et al. (2019) reported that orexinergic neuronal dysfunction is involved in sleep waking, circadian rhythm disturbances, and abnormal network activity in mouse models of HD [114]. However, no significant sex differences have been reported for HD, and we therefore expect further research to focus on this aspect. Furthermore, serum orexin-A levels have been shown to be significantly reduced in patients with multiple sclerosis, which is associated with the severity of symptoms and a decrease in serum brain-derived neurotrophic factor (BDNF) and melatonin levels [115,116]. However, sex differences have not been reported, and further research is therefore required.

Given the intricate interplay between orexin levels and the pathogenesis of neurodegenerative diseases, further research is warranted to clarify the specific mechanisms of action of orexin in the neurodegenerative process, and to investigate how orexin affects the clearance of beta-amyloid and tau proteins, as well as the association between this pathological process and disease progression. The role of sex differences in orexin expression and its impact on neurodegenerative diseases should not be overlooked. Future research should focus on elucidating the potential mechanism underlying this phenomenon, and exploring its potential value for disease diagnosis and treatment. In addition, although selective orexin receptor antagonists have shown potential in improving neurodegenerative disease-related symptoms, their efficacy and safety remain to be validated through large-scale clinical trials.

4.7. Drug addiction

The orexin system holds a pivotal position in orchestrating various addiction-related behaviors [117]. Experiments have extensively documented the role of the orexin system in drug addiction, encompassing its participation in addictions to cocaine, alcohol, opioids, and nicotine [117]. Drug addiction is further correlated with variations in the quantity of orexinergic neurons [118,119] and *orexin* gene expression [119].

OX_1R blockade(SB-334867) potently attenuated orexin-mediated cocaine seeking during reinstatement in male rats, but had no effect on female rats, indicating that OX_1R signaling modulated cocaine seeking and differed between the sexes in cue-induced reinstatement [120]. However, researchers who studied the effect of an OX_1R antagonist on methamphetamine seeking did not report sex differences [121]. They found that the OX_1R antagonist(SB-334867) reduced the response to methamphetamine cues in both adolescent and adult male and female rats. However, the causes for this inconsistency remain unclear. Absi et al.(2019) further reported a sex-specific role of orexin in the process of smoking cessation [122]. Circulating orexin levels were negatively correlated with withdrawal symptoms, but positively correlated with craving symptoms in women; however, the opposite pattern was observed in men, with orexin levels showing a positive correlation with withdrawal symptoms and a negative correlation with craving symptoms, indicating that sex serves as a crucial moderator in the relationship between orexin and addictive behaviors [122]. Furthermore, OX_1R showed sex-related differences in the regulation of alcohol intake behavior. Treatment with the OX_1R inhibitor SB-334867 was found to reduce binge alcohol consumption in male mice, but not in female ones [123]. In addition, OX_1R plays a complex role in different motivational behaviors such as more extensive motivational behaviors in males and stress-related behaviors in females [123].

A recent study investigated the incubation of methamphetamine-seeking following a 30-day period of forced abstinence, revealing that female rats exhibited higher levels of OX_1R and OX_2R receptor mRNA in the nucleus accumbens than male rats. Furthermore, methamphetamine-seeking behavior in females, as opposed to males, was found to be negatively associated with mRNA expression levels [124].

In summary, the orexin system, particularly the receptor, OX_1R, exhibits significant sex differences in the process of drug addiction. These differences are not only reflected in different types of addictive drugs, but also manifest in various stages and expressions of addiction. Therefore, it is imperative to consider sex differences thoroughly to formulate more accurate and effective intervention measures for drug addiction.

5. Conclusion

The orexin system plays a vital role in many physiological activities, such as sleep/wake cycles, pleasure from activity, food intake, sexual behavior, drug addiction, stress, cognitive flexibility, and monoaminergic neurotransmission. They also play crucial roles in the development of neuropsychiatric disorders. Preclinical and clinical studies have shown that the orexin system exhibits sexual dimorphism, which is further observed in patients. This review delves into the latest progress in research on orexins and their roles in neuropsychiatric disorders. These findings reveal how orexin levels influence the occurrence, progression, and clinical manifestations of neuropsychiatric diseases and suggest that orexin modulators have potential as therapeutic agents. It is obvious that sex differences of the orexin system are closely linked to reproductive hormones. Notably, several studies have shown that the orexin system affects the cognitive flexibility of rats subjected to restraint stress through its effect on the HPA axis. However, further research is required to

determine the exact mechanisms and upstream partners involved. Given that few studies have been conducted in this area, our findings suggest that further efforts are required to elucidate the underlying mechanisms. With the development of artificial intelligence and big data analytics, it is believed that future orexin research will increasingly rely on data-driven discoveries. By integrating multi-source data, including genomics, transcriptomics, metabolomics, and clinical data, researchers can uncover the differences in the orexin system among various populations, providing strong evidentiary support for precision medicine. Finally, if the gaps in our knowledge regarding how sex differences affect the functions and behaviors influenced by orexin can be filled, it is promising to develop new ways to diagnose and treat human health issues.

Data availability

No data was used for the research described in the article.

CRediT authorship contribution statement

Jinghan Zhang: Writing – original draft, Investigation. **Kangyu Jin:** Writing – review & editing, Conceptualization. **Bing Chen:** Writing – review & editing. **Shangping Cheng:** Methodology, Investigation. **Jinfan Jin:** Investigation, Writing – review & editing. **Xiaolan Yang:** Writing – review & editing. **Jing Lu:** Writing – review & editing, Conceptualization. **Qinghai Song:** Writing – review & editing, Conceptualization.

Declaration of competing interest

The authors have no conflicts of interest to disclose.

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