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Orexins' Brain Cellular Connectivity and Therapeutic Potential in Addiction

Awgichew Shewasinad Yehualashet [1]*, Berhan Begashaw Yikena[1], Abera Hadgu Berhe[2] and Birhanetensay Masresha Altaye[1]

1 Department of Pharmacy, Pharmacology and Toxicology Unit, College of Health Sciences, Debre Berhan University, P.O Box. 445, Debre Berhan, Ethiopia
2 Department of Pharmacology, College of Health Sciences, Mekelle University, P.O. Box 1871, Mekelle, Ethiopia

Corresponding author:
Awgichew Shewasinad Yehualashet

Department of Pharmacy, Pharmacology and Toxicology Unit, College of Health Sciences, Debre Berhan University, P.O Box. 445, Debre Berhan, Ethiopia

awgshewa@gmail.com

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Abstract

Addiction is a disorder of brain reward system, motivation and memory manifested by certain biological, psychological, and social problems. The Lack of most effective and long-term pharmacotherapies that can improve quality of life, necessitate the need to understand the biology of addiction for possible identification of drug targets in the brain circuit and conduct large-scale clinical studies with the hope of finding efficacious and safe medicines. Because of the wide projections of orexinergic neurons and their complicated linkage with other neurons along with the diffused distribution of orexin receptors, the orexin system is involved in the regulation of multiple central nervous system functions including addiction. Rigorous studies on the molecular and cellular bases are highly important emphasizing on how the orexinergic system is interacting with addictive substances and can modify the brain reward circuit. Therefore, the aim of this review is to discuss the existing knowledge and evidence on orexin's cellular connectivity with addiction-related brain structure and the emerging role of orexinergic system in the treatment of addiction.

Keywords: Orexins; Hypocrteins; Addiction; Reward system; Signaling

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Introduction

Addiction is a chronic relapsing disorder manifested by compulsion to seek and take drugs, loss of control over drug intake, and emergence of a negative emotional state. The established symptoms of addiction are because of a motivational withdrawal syndrome when the access to substance use is prevented. Mainly, it is disorder of brain reward, motivation, memory and related circuitry of the brain with biological, psychological, social and spiritual problems [1,2]. This problem of the brain is usually as a result of either from the use of controlled drugs or their use to replace non drug related behaviors in addition to the direct positive or negative reinforcing effects of the drug [3].

The escalated drug use which is beyond the occasional, limited, recreational use of a drug clinically results in loss of control over drug intake, and emergence of compulsive drug-seeking behavior which produces allostatic changes in the brain reward and stress systems and follows binge/ intoxication, withdrawal and anticipation. Positive and negative reinforcement have been identified to play a role in this allostatic change during addiction. Positive reinforcement is the process by which presence of a stimulus enhances the probability of a response whereas negative reinforcement is removal of an aversive increases the probability of a response [4].

Rewarding System and Brain

Reward particularly is identified by individual's response to stimuli which brings about pleasure and arousal. The persistent, compulsive and uncontrolled behaviors of addiction are maladaptive and destructive. Reward encompasses activities beyond non-alimentary and nonsexual functions like gambling and because of its diversified behavior, rewards trigger agents to search for and trading in market [5].

Although there are several evidences supporting the idea that the brain's mesencephalic dopaminergic system is responsive to rewards, no solid evidence is available to illustrate its role

in the process of reward [6]. However, it has been shown that dopamine (DA) is involved in the hedonic component of reward. Certain evidence showed rewards can elicit an increase in the activity of dopamine, but there are some scenarios whereby this activity of dopamine does not happen. That is why; several hypotheses have been proposed to make a different mechanism [7,8]. For instance, as per the prediction error hypothesis, it is plausible that the change in the function of DA neurons encode information interpreted wrongly of the amount and time of reward [9-11].

Addictive drugs are both rewarding and reinforcing. Substance use disorders are linked significantly with the prevalence of mood and anxiety disorders happened independent of intoxication and withdrawal [12,13]. For example, alcohol overconsumption is mostly associated with anxiety and depression. Animal models showed that administration of acute ethanol results in a dose-dependent anxiolytic effects that lasts for short period, but increasing acute high doses ingestion produce withdrawal-induced anxiety. Additionally, greater alcohol intake has been associated with states of anxiety [14-16].

After realizing the arrangement of brain loci and tracts by Wise and Bozarth, it was constituted with a neural circuit synaptically connected neuronal elements. The connected elements are; a descending link extending from the anterior bed nuclei of the medial forebrain bundle to the ventral tegmental area (VTA), an ascending link ranges from the VTA to the nucleus accumbens, and a further ascending link from the nucleus accumbens to the ventral pallidum [17,18]. Drug induced behaviors are a consequence of the activation of the three neuronal system mentioned above by the addictive drugs from different pharmacological groups. For instance, the addictive drugs barbiturates, benzodiazepines, cannabinoids, ethanol, nicotine, and opiates act upon synapses linked with VTA whereas amphetamines, cannabinoids, cocaine, opiates, and dissociative anesthetics act upon synapses involving the nucleus accumbens [19].

The capacity of the brain to reorganize itself by forming new neural connections are mostly triggered and maintained by neuronal adaptations that interacts with genetic and environmental vulnerability to addiction. Signaling mechanisms and alterations in gene transcription have been observed in binge/ intoxication. For instance, chronic exposure to many abused drugs upregulate cAMP formation, cAMP-dependent protein kinase A (PKA) activity, and PKA-dependent protein phosphorylation in the nucleus accumbens [20]. Several interventions that highly activate nucleus accumbens cAMP/ PKA signaling enhance increment in drug self-administration or compulsive-like drug-seeking behavior. It is the up regulation of a postsynaptic Gs/cAMP/PKA signaling pathway in the nucleus accumbens which might involve in the neuroadaptation linked to the establishment and maintenance of the state of addiction [21]. Substance use chronically increases the activation of cAMP response element binding protein in the nucleus accumbens, but not in the central nucleus of the amygdala. Consequently, the introduction of cAMP response element binding protein in the nucleus accumbens reduces the reinforcing value of rewards and this change might contribute to withdrawal/negative affect stage-related decreases in reward pathway function [22,23] .

Seeking of food or water is a learned goal oriented motivation because of selective reinforcement of initially random movements. Once stimulus-reward associations have been formed, they can remain potent for some time even after the reward has been underestimated because of hunger or thirst, or the dopamine system is blocked [24,25]. After a habit has been established, it will take control of our body with unless the conditioned stimulus is extinguished and voidance of the conditioned significance of stimuli could be by a repeated actions without reward, trials with the help of neuroleptics [26].

With the idea that dopamine is to be important for functions of learning and memory, starting from many years back, experimental psychologists have been developing and refining behavioral models of addiction. Addiction, a neurobiological disorder as of a repeated substance abuse encodes an error to the regular circuitry of the rewarding and adaptive behaviors results in drug-related neuroplasticity. According to some findings, addictive drugs have shared similarities in that; they can enhance the effects of the midbrain DA function, specifically at the level of their terminals in the nucleus accumbens. Cocaine, a monoamine blocker, is among the drugs that activate dopamine system, binds with greatest affinity to dopamine transporters there by can participate in removal of dopamine from synapses. Transporters blockage can enhance the efficacy of dopamine, therefore, it reveals to be the cause of cocaine addiction [5,27].

Drug addiction leads to substantial disturbances in an individual's behavior that usually end up with isolation, marginalization, or incarceration of the individuals. As a consequence of stress of social isolation, it is most likely to result in changes in stress circuits, higher vulnerability to drug use and relapse. Therefore, any treatments modalities for addiction should consider not only the neurobiological changes but also the social aspects of the addict. Because of its chronicity, long-term treatment for addiction is usually necessary and it is an ongoing area of investigation [28-30].

For the last decades, many treatment targets had been identified following the discovery of signaling molecules in the brain which were assumed to be essential to express addiction-related behaviors in animals [31]. Many proposed pharmacotherapies of addiction, however, are not well successful and the current clinical practice is limited to only some addictive drugs [32-35]. To date, the therapeutic approach for addiction is highly relied on psychological and physical rehabilitation approaches. The addicted patients are usually separated from their family and people, and are hospitalized in special rehabilitation centers. In the treatment modality the therapeutic objectives are; terminating drug usage, staying drug free and becoming more productive in life. Finding the most effective treatment is challenging and different for every individual. The most effective treatment approaches include detoxification, behavioral counseling, use of medications (for drugs like opioids, tobacco and alcohol addiction), treating concomitant metal illnesses and long-term follow-up to prevent relapse [36,37]. Because part of the addicted patients experiences relapse right after they have returned to their environment, these treatment strategies are not as effective as desired and are still problematic. Many other studies including and orexin based therapies have been

listed by the National Institute on Drug Abuse's (NIDA) Division of Therapeutics and Medical Consequences as a high priority treatment target for drug abuse indicated that the orexinergic system is one promising drug target for treatment of addiction [1,34,35].

Orexinergic System in Addiction

Orexins/hypocretins are excitatory neuropeptides produced by neurons that are found exclusively in three hypothalamic areas of the brain: Lateral Hypothalamus (LH), perifornical area and dorsomedial hypothalamus [38]. These orexinergic neurons, representing relatively a small number of cells, are projected extensively to different areas of the brain and are suggested to play role in various physiological functions, such as arousal, cognition, stress, appetite, metabolism and addiction. The notion of implicating orexinergic system in the neurocircuitry of addiction was initially assumed from studies involving their involvement of orexin in natural rewards such as food and sex and orexinergic projections to structures of the reward-addiction pathways [39].

Different molecular elucidations show that the molecular composition of hypothalamic neurons includes peptide hormones. Neuropeptides are the most prominent groups of these regulator molecules [40]. About 40% of the clones encoded neuropeptide transmitters; the hypothalamus is recognized in making intracellular signaling molecules [41]. One of such peptide transmitter is prepro orexin (prepro hypocretin) which was identified using a subtractive polymerase chain reaction (PCR) technique. Further cloning of cDNAs reputed to encode a protein with 130 amino acids (AAs) resulting two peptide products; hypocretin-1 and hypocretin-2, having structural resemblance to each other were identified in 1998. The same peptides, named OXA and OXB, recognized as the ligands for two orphan G protein-coupled receptors (GPCRs): orexin receptor 1 and 2 (OX1 and OX2 receptor) [42,43]. OXA is composed of 33-AA, with an N-terminal pyroglutamyl residue and C-terminal amide moiety, whereas, OXB is a 28-AA, C-terminally amidated linear peptide. Molecular mass and sequencing analyses studies indicated that the four Cys residues of OXA formed two sets of intrachain disulfide bonds (Cys6-Cys12, Cys7-Cys14). The amino acid sequence between OX1 and OX2 has homology of about 64% and it was later realized that prepro-orexin is identical to prepro-hypocretin and that OX A and B correspond to hypocretin1 and 2, respectively [44,45]. OXRs are grouped under the GPCR, specifically to the rhodopsin family. OX1 receptor contains 425 AAs with sequence homology of about 91–98% between humans and rats. OX2R is slightly larger, with 444 amino acids. Expression system investigations showed that OX2R has equal affinity for OXA and OXB, while OX1R has a ten times higher affinity for OXA [46].

Orexin cell connectivity with addiction-related structure

In human brain, it is estimated that there are approximately 70,000 orexinergic neurons which send projections to almost all parts of the brain except the cerebellum as depicted in **Figure 1**, implicating for their multiple physiological roles [47,48]. The monoaminergic and cholinergic nuclei receives dense projections from the brain and spinal cord. Other neurons receiving the projections also include the noradrenergic neurons of the locus coeruleus (LC), the serotonergic neurons of the dorsal raphe nucleus (DR) and median raphe nucleus (MnR), the histaminergic neurons of the tuberomammillary nucleus (TMN), and the cholinergic neurons of the laterodorsal tegmental nucleus (LDT) and pedunculo pontine tegmental nucleus (PPT) [49-51].

Interactions of orexin with accumbens

The nucleus accumbens (NAcc) receives dopaminergic input from the VTA and orexin containing terminals from the lateral hypothalamus. In addition, orexin receptor 2 was expressed in Nacc. An investigation on the effect of orexins on synaptic transmitters of the NAcc showed that orexins decrease the amplitude of NMDA currents and enhances GABAergic conductances in NAcc neurons. In the NAcc, it is not well investigated on what behavioural roles orexins could influence. The hypocretins are known to stimulate dopaminergic neurons in the VTA, major sources of afferents to the NAcc. The NAcc is known to play a role in motivated movements and drug-seeking

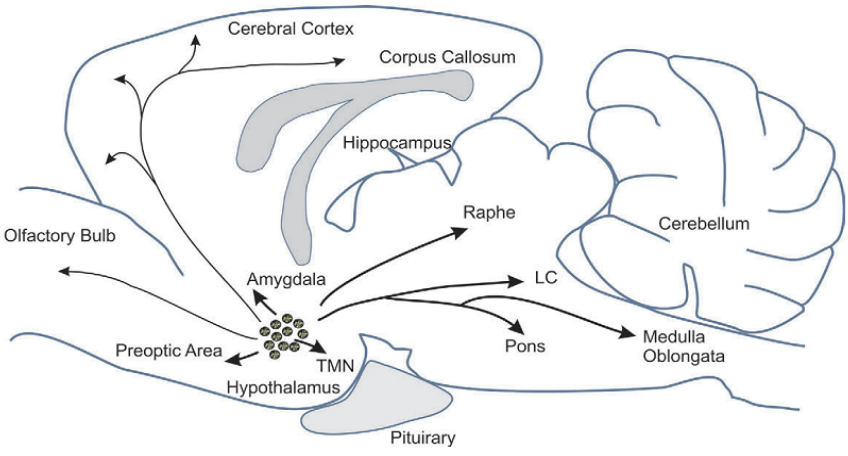

Figure 1 Projections of orexinergic neuronal system in sagittal section of rat brain [51].

behaviour. In this regard, we find it highly suggestive that the hypocretins act in NAcc like ethanol, which also reduces NMDA currents and enhances GABA response [52,53].

Interactions of orexin with paraventricular nucleus

Attention was given to the paraventricular nucleus of the thalamus (PVT) since it has linkage with the limbic and cortical structures that are part of the neurocircuitry that can mediates drug seeking behaviour. The PVT is involved during cocaine seeking behaviour initiated by the presence of cocaine predictive stimuli [54,55]. Some important elements of the neurocircuitry of addiction can receive projections from PVT, majorly from the posterior region, implicating the potential role of this thalamic nucleus in the regulation of compulsive drug seeking that characterizes addiction. Among the wide projections that can originate from the PVT, specifically, those directed to the hypothalamus projections are interesting in that the PVT could influence behaviour [56].

A study [56] found that the discrete administration of OrxA in the pPVT elicited a priming effect that reinstated cocaine-seeking behaviour in dependent animals at 2-3 weeks but not at 4-5 weeks of abstinence. The activation (or lack of activation) of Orx-producing neurons in the lateral hypothalamus (*LH*), dorsomedial hypothalamus (*DMH*), and perifornical area (*PFA*) paralleled OrxA's priming effect (or lack thereof), suggesting that recruitment of the LH/DMH/PFA is essential for the manifestation of cocaine-seeking behaviour. The connectivity of the PVT/LH/DMH/PFA circuit appears to undergo significant neuroadaptations during abstinence. It was suggested that future studies will be necessary to investigate the molecular changes (e.g., Orx and Orx receptor production) that may exist with cocaine dependence and prolonged periods of abstinence and this kind of studies may reveal potential treatment targets for persistent vulnerability to relapse associated with cocaine dependence.

Studies have demonstrated the role of the posterior PVT and particularly Orx transmission in cocaine seeking behaviour [54,55]. Fewer γ-aminobutyric acidergic neurons are found in local PVT circuitry, suggesting that the synaptic network is majorly glutamatergic in this midline nucleus. Neurons in the PVT receive heaviest Orx projections in the brain, and Kappa opioid receptor (KOR) immunoreactivity is high in these neurons. In the PVT, Orx and Dyn modulate ionic conductance and neuronal activity in opposite directions [57].

Interactions of orexin with insular

The insula, an area in the cortical brain region, engages in regulating interoceptive information associated with motivational and emotional states to promote physiological homeostasis. This part of the brain may also participate in the regulation of experience of conscious urges and cravings [58]. A recent report indicated that any damage to this brain region in human smokers showed a remarkable change in tobacco addiction distinguished by spontaneous cessation of the smoking habit and a reduced desire to smoke then after [59]. However, the neurobiological mechanisms by which the insula regulates the persistence of the tobacco habit remain unclear. A study [60] tested the orexin transmission at orexin 1 receptors in the insular cortex to see how it regulates nicotine reinforcement and it was observed that dense innervation of orexin 1 peptide containing neurons into the insula. It was also shown that the expression of orexin 1 receptors within this brain region. Furthermore, direct administration of SB-334867 into this brain region showed to attenuate nicotine self-administration.

Orexin cells activation by drug cues

In order to carry out the mechanisms of addiction, reliable animal models that can show key features of the human phenomenon are relevant. Auspiciously, there exists a pattern of behavior that mimics various aspects of human drug addiction which is not applicable for other psychiatric problems [61-63]. Among many functions exhibited by OXs, one which arouses curiosity is their role in the reward system. OX containing neurons projected from the LH to the VTA, the brain regions that comprise the mesolimbic "reward pathway". Recently, OXRs have been implicated in the motivational drive for addictive substances, such as morphine, cocaine, alcohol, etc [64].

Different findings suggested that people with narcolepsy rarely became addicted to the potent stimulants while used to treat disorders at the time. Perhaps, some researchers speculated that OX contributes to the emergence of drug abuse. An observational animal study by Drs. Harris and Aston-Jones showed that the LH cells in the same area as OX neurons were activated during drug seeking using a behavioral assay. Rats in one test cage were allowed for a repeated morphine injection while rats in the other cages were administered with saline. It was observed that, rats in the first cage were tended to move to the drug paired area in an effort to re-experience the opiate effects. The time rats spend in the area for their morphine place preference indicates the intensity of the drug to motivate drug seeking behavior [61].

Another study has implicated reinstatement of drug seeking behavior in response to conditioned cues associated with alcohol appears to activate hypothalamic neuropeptide neurons, such as OXs. The release of OXs into the VTA promotes drug-cue associations by triggering the entry of NMDA receptors into the excitatory post-synaptic membrane of dopaminergic neurons on the VTA. This occurs through a PKC-dependent mechanism, and is essential for the ability of drug-cues to induce addictive behaviors in animals that are believed to model relapse to substance use [24]. In addition, there are experimental observations highlighting the potential role of OXs in addiction in that, the low CSF OX-A levels in patients with narcolepsy and lack of dependence in these patients despite receiving amphetamine treatment. It was also demonstrated that OX knock-out mice display attenuated morphine dependence and other recent finding have also showed that blockade of the OXR1 reduces self-administration of alcohol, nicotine and high-fat food [65, 66].

Self-administration of cocaine with the intermittent access procedure produces a strong addiction like state that is orexin dependent. A similar study [67] conducted in determining the role of the orexin system in opioid addiction using intermittent access self-administration of fentanyl showed an increase in fentanyl intake, increased motivation for fentanyl on a behavioral economics task, persistent drug seeking during abstinence, and

stronger cue induced reinstatement. The finding also reported that orexin-1 receptor antagonist SB-334867 reversed the addiction behaviours induced by intermittent access to fentanyl, which was associated with a persistent increase in the number of orexin neurons. This finding signified that the intermittent access model is an important strategy in the study of opioid addiction and that the orexin system is pivotal for the maintenance of addiction behaviors induced by intermittent access self-administration of fentanyl.

The orexin-1 receptor (Ox1R) antagonist SB334867 (SB) reduces seeking of drug reward under conditions of high motivation. There is some evidence that the effects of systemic SB on reward seeking persist beyond the pharmacological availability of the drug, however the time course of these effects is not well characterized, nor is it known whether similar persistent effects are observed following intraparenchymal injections. A study [68] done to examine the persistent effects of acute systemic and local treatment with SB on motivation for the short-acting μ-opioid receptor agonist remifentanil showed that systemic injections of SB immediately prior to behavioural testing reduced remifentanil motivation. The effect was sustained on a subsequent test at 24 h, but not on a third test at 48 h. This study indicated that the effects of SB on opioid seeking behaviour persist beyond the bioavailability of the compound. These observations have important ramifications for the future clinical use of orexin receptor antagonists for the treatment of addiction.

Efficacy of orexin receptor antagonists in reducing seeking of opioids

A visible role for OXR1 signaling has also been observed in the establishment of behavioral sensitization to psycho-stimulants. For example, SB-334867/ OX1R antagonist/ treatment sensitization following repeated cocaine and amphetamine treatment, in comparison, OXR2 signaling appears to primarily mediate wakefulness and arousal and play less of a role in mediating reward seeking, however, infusions of OXB (presumably acting on OXR-2) into the VTA increases preference for morphine and repeated cocaine exposure produces an up-regulation of OXR2 levels in the nucleus accumbens. It is also worth highlighting recent evidence that blockade of the OXR2 can prevent ethanol self-administration, place preference and reinstatement [64].

Stimulation of OX neurons in animal models reinstates previously extinguished drug-seeking behavior, which reveals the role of OX neurons in describing the most commonly observed drug seeking behavior in drug addicted patients following a period of withdrawal [69]. OXR antagonist SB-334867-A administration delays recovery of drug-seeking behavior in the presence of events associated with cocaine or heroin, but it does not affect relapse induced by the drug itself. These findings implicate a scientific ground to consider OX1R receptors as potential drug targets in the treatment of relapse associated with the addiction of alcohol, morphine, or nicotine. OXR antagonist administration does not block cocaine seeking behavior induced by cocaine itself [70,71]. This is contrary with the ability of SB334867 to block cocaine seeking induced by the environmental cue. The most important consequences of the study are focus on the selective OXR antagonists which may be used as therapy to prevent relapse and compulsive drug-seeking behavior [72].

If OX signaling pathways promote craving, then the use of antagonists of one or both OXRs should reduce substance craving and relapsing in clinical practice. OX antagonists currently being developed are to address mainly sleep disorders. Although their kinetics may not be optimal in the treatment of addiction, there are some promising findings. For example, Almorexant, the first competitive and dual OX antagonist of both OX1 and OX2 receptors that selectively inhibits the functional consequences of OX1 and OX2 receptor activation, such as intracellular Ca2+ mobilization (DORA), reduces CPP for cocaine and amphetamines [73]. In animal models, Almorexant also showed a reduction in alcohol consumption in mice and rats. However, Simple Orexin Receptor Antagonists (SORA) for OX1 and OX2 receptors appear to be more promising in the treatment of addictive disorders [74,75].

In some other preclinical tests with animal models, antagonism of OX1R showed attenuation of opioid, psychostimulant, alcohol, and cannabinoid relapse behavior. Similarly, OX2R antagonism has also shown to reduce opioid and alcohol self-administration [76]. Without even knowing the precise differences of orexin's function on different substance classes, the current position of the antagonists in addiction research is encouraging. In certain types of addictions, a 2-SORA or DORA treatment might be advised, although data on these two groups of antagonist is still lacking and paradoxical. This is the rationale behind OX1R to be the primary target as far as it does not come up with (any known) side effects, like blockage of the OX2R. Based on the current data and few animal experimental studies, the OX system is a promising target for the treatment of addiction. Not only plays role in different addictions, but also a single treatment method could potentially affect more than one addiction [36].

Off target effects of orexin receptor antagonists

Interestingly, orexinergic neurons show connections to regions involved in cognition and mood regulation, including hippocampus. Orexins enhance hippocampal neurogenesis and improve spatial learning and memory abilities, and mood [77]. Various findings indicated that the orexinergic system contributes significantly to mediation of stress, as well as anxious and depressive behaviour. These lines of evidence are reason enough to posit that pharmacotherapies involving the orexin/ hypocretin neuromodulators and hormones may be beneficial in patients with anxiety and depression. While the orexinergic system has two active neuropeptides, OrxA and OrxB, it appears to be the receptors, Orx1 and Orx2, which primarily give rise to opposing functions relative to stress and affective behaviours. In keeping with the theme of this special issue, antagonists do have potential for limiting Orx1 receptor generated anxiety and panic [78].

Preclinical studies demonstrated that female rats have a higher demand at null cost for all three of the palatable rewards though sex differences in motivation to obtain the rewards was not clear. The behavioral differences probably associated with differences in expression of the hypothalamic neuropeptide orexin between male and female rats; however, orexin receptor-1 blockade

generally reduces null cost and motivated responding for palatable food in both sexes [79].

Future perspectives

Because of wide projections of orexinergic neurons and their complicated linkage with other types of neurons along with diffused distribution OXRs, the OX system is involved in the regulation of multiple CNS functions including addiction [80]. To date, OXs are among the targeted neuropetides for addiction. The neural signaling pathways of OX system have been largely and intensively studied since their discovery. However, the role of this system in neuropsychiatry and the neural mechanisms in mediating these disorders is still not well understood. Finding novel functions of orexinergic system is future active area of investigation [43,80].

Traditional drugs used in the treatment of addiction are still with side effects and researchers are looking for additional options. Strategies targeted to OX system, such as gene therapies or neural stem cells transplantations, are also a valuable methods. The recent technology, optogenentics, aimed in the control of neuronal activities has also been successfully applied in the control of neurons in amygdala of the brain. It is worth extending the use of optogenetics to target OXs and associated systems and developing novel methods to treat OX mediated neuropsychiatry diseases [81,82]. The functional perspectives of OX neurons through input output analysis is another important future research goal to be implemented. Few studies have shown VTA is one possible target of OX neurons for their reward effects and some studies as mentioned previously, illustrate OXs role in reward-related processes in accumbens, PVN and insular cortex as well. It is also important to study the effect of orexinergic projections on other brain areas which probably have an effect on reward and related functions.

Behavioral effect implication is also a scientific research question to be evaluated. The two OXRs (OX1R and OX2R) respond differently for reward and arousal. Because the effect of each receptor in many areas of the brain is dominantly observed, it requires further investigation and scrutiny. Prior studies found that orexin is important in behavioral responses to opiate withdrawal even though its implications in behavioral functions have not been well studied [83,84].

OXA acts mainly through OXR1 to increase the synaptic efficacy of the dopaminergic VTA neurons promoting dopamine-release which is related to seeking behaviors and reinforcing effects of drugs of abuse. The stimulation of the orexinergic system by stress is linked with neuroadaptative changes that lead to an increased susceptibility to drug addiction and relapse. The tendency of response of OXR antagonist to each addictive substance is not well studied [36,69]. Therefore, further investigation will have a paramount importance in identifying OXR antagonist with respect to each substance of abuse.

Different reviewed animal studies indicate that OX neurons and receptors represent an important new target for clinical interventions in a variety of disorders. Drugs to interfere with OXRs are not only being developed for addictive disorders, but also such drugs should be proved for their use in mood disorders, given the role of OX in reward, hedonics and motivation. Additionally, orexinergic drugs could also have a potential role for treating deficits in learning, and other cognitive disorders such as dementia [85-87].

The potential attractiveness of neuropeptide receptor systems as therapeutic drug targets for neuropsychiatry disorder is rising by their high level of signaling specificity as well. Expression of neuropeptides is often restricted to small populations of neurons within a small number of brain nuclei including orexins (OXs). Neuropeptides mostly bind to their receptors with high affinity and specificity because of their large allosteric binding sites. These characteristics suggest that therapeutic drugs which target neuropeptide systems may be less prone to undesirable and nonspecific side effects in comparison to the current drug treatments of vast neuropsychiatry disorders [88,89]. In general, orexins are necessary for maintenance of health as these peptides control and organize important homeostatic functions directly or indirectly. Orexins can mediate metabolic regulations in addition to their role in brain regions [77]. This signals that orexin system is not only a promising target for treating addiction but also for many other diseases.

Disclosure

The authors report no conflicts of interest in this work.

Author Contributions

All authors made a significant contribution to the work reported and have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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