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Research Article

Hipocretinergic/Orexinergic System and its Role in Drug Addiction: A Narrative Review

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Abstract

Background

Addiction treatment commonly presents therapeutic failures. In recent decades, there has been a growing interest in neuropeptides and their role in regulating the different phases of the addictive process. Such neuropeptides include Orexin, also known as hypocretin.

Objective

The objective of this review is to analyze the recent evidence on the orexinergic system, its role in addiction reinforcement and recurrence, and its therapeutic implications.

Methods

A PubMed, Ebsco, Lilacs and SciELO search was performed using MesH terms based on the title. Articles in English, Spanish, and Portuguese were included.

Results

The orexinergic system is involved in the Incubation of drug seeking after a protracted abstinence period. Orexin and glutamate in VTA are necessary simultaneously for the reinstatement of cue and stress-induced cocaine and alcohol consumption.

Conclusion

The orexinergic system is key in the drug reward and seeking pathways and is a therapeutic target for future drug therapies in addictive disorders. A better understanding of this system will allow effective interventions to prevent relapse in drug addicts.

Keywords: Hypothalamus; Orexin; Relapse; Review; Reward; Substance related disorders

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Introduction

Psychoactive substance use disorders PSUD are characterized by compulsive drug-seeking and ingestion, loss of control in suppressing continued substance use, andnegative emotional states when the drug is not available [1]. It is considered a chronic disease with a high relapserate that may be aroused by the substance itself, re-exposureto drug-related cues, and/or stressful events following a period of withdrawal [2]. Addicts are persistently vulner able to relapse in drug use following months oreven years of abstinence, and relapse is considered the most important problemin addiction treatment [3]. Treatment for addiction to substances such as cocaineand heroin, often presents treatment failures and a high percentage of addicts relapse after period of abstinence that can last days or years [4,5]**.** Given the lack of adequate treatment to avoid relapse, addiction to PAS is an enormous social, economic, and medical burden all over the world [6,7]**.** Neuroanatomical substrates and neurochemical mechanisms associated to relapse have been widely studied over the past 15 years; however, we still lack full understanding of the underlying neurobiological basisand there are important knowledge gaps with regards the topic. Recent decades have witnessed a growing interest in neuropeptides and their role in the regulation of the different phases of the addictive process [8]**,** among which orexins orhypocretins, that seem toplay a central role in the regulation of the reinforcing effects of PAS, as well as in withdrawal and relapse [9,10]**.** Thus, the pharmacological management of the system represents a potential therapeutic target for the treatment of patients with PSUD [11]**.** Over the past five years, there has been a significant increase in research work that has attempted to clarify the role of orexinsin the different facets of the substance-addiction process. This has made it necessary to update and reexamine the evidence in order to make advances in terms of the neurobiology of addictions [7]. As such, the purpose of this narrative reviewis to analyze the recent evidence on the role of the orexinergic systemin addiction reinforcement and recurrence together with the therapeutic implications of this knowledge.

Materials and Methods

For this narrative review, a search was undertaken in Pubmed, initially of original works on animals and humans that describe the neurobiological mechanisms of addictive behavior and, secondly, of articles from the first publication by De Lecceaand Sakuray in 1998 who described the role played by orexins in animal models and clinical trialsused to asses the role of substances that modify the orexinergic systemin the treatment of PAS addiction. For the first phase

of the search, the following keywords were used: Addict* or "Substance-Related Disorders" or "behavior, addictive" or "drug addiction" and "neurobiology" and all relatedMesH terms. For the second phase, the following keywords were used: "orexins/hypocretins" and addict* or "Substance-Related Disorders" or "addictivebehavior" or "drug addiction" and all related MesH terms. The search included articles in English, Spanish, and Portuguese published up until December 2016. Articles on addiction to alcohol, nicotine, amphetamines/cocaine, and opioids were included as were experimental studies on animals that examine the role of orexins in the different phases of the addictive process. Articles related to the topic, which appear in Pubmed and the references of interest found in each of the articles included were also traced.

A PubMed search was conducted, adapted to the search criteria of databases Ebsco, Lilacs, and SciELO. Review articles on the topic were excluded. A qualitative analysis was conducted involving the results of the most relevant articles in terms of the role of orexinsin theaddictive processfrom the perspective of self-administration/extinction/reinstatement, conditioned place preferenceandlocomotionanimal models that are the most frequently used in research on addictions.

Results

Orexins and their physiological action

Orexin Aand Orexin B (hypocretin 1 and hypocretin 2) are recently discovered peptidesproduced basedon the prepro-orexin molecule synthesized only in hypothalamic neurons [12]. Since its almost simultaneous discovery by Lecea et al., and Sakurai et al., in 1998 [13,14], a considerable number of studies have been carried out to characterize this new system of neuropeptides. Orexin Ain mammals is a peptidewith 33 amino acids with two interchain disulfide bridges, a molecular weight of 3562 Da, apyroglutamyl residuein its extreme N-terminal and amidated in its extreme C-terminus (both typical neuropeptide terminals). The primary structure of Orexin Ais completely conserved among humans, rats, mice, pigs and cows; whereas Orexin B is a 28 amino acid polypeptide with an amidated C-terminus and a molecular weight of 2937 Da, with 46% de homology (13/28 a.a) compared to the amino acid sequenceof Orexin A [15], Both Orexin Aand Orexin Bare peptidesderived from a common precursor: Prepro-orexin, codified by a gene composed of two exonsand one intron that separates them, located inchromosome 17q21 in humans. Prepro-orexinis apolypeptideof 130-131 amino acid residues (depending on the species-131 in humans), with a typical secretory signal sequencein its extreme N-terminal and cleavedto the mature forms of Orexins A and B [16]. Sakurai et al., also characterized 2 metabotropic receptorsfor this system, called Ox1R and Ox2R. Ox1R is attached exclusively to the Gq protein, whereas Ox2R can be joined to both Gi/o andGqproteins [17]. Although Orexin 2 has the same affinity for both receptors, the affinity of Orexin 1is 10-fold higher for Ox1R than for Ox2R [14], Orexin neuronsare widely projected throughout the neuro-axis, including innervation of the prefrontal cortex, hippocampus, thalamus, midbrain, and thespinal cord [18,19]**.** Similarly, the two orexin receptors are widely distributed throughout the Central Nervous System (CNS), but they are regionally selective [20,21]. This complex distribution of their projections allows the orexinsto participate in a variety of homeostatic functions: Predominantly eating behavior and arousal [22,23]**.** The growing interest to study the actions of the orexinergic systemhas led to the development of orexin receptor antagonists, that have been used in different experimental studies to clarify the pharmacological effects of the seneuropeptides [24,25]**;** among them the orexin receptor antagonist A SB334867 [26], and the dual Orexin A and B receptor antagonist Almorexant [27].

This system was the object of great interest in the years following its discovery when it was discovered that the dysfunction of this system was strongly associated to symptoms of narcolepsy in animals [28-30] and subsequent works involving humans showed that patients with narcolepsyhad a small quantity of orexinin their Cerebrospinal Fluid (LCR), and presented a loss of most of their orexigenic neurons [31]. With these findings, the interest in orexins focused on the activation or arousal and maintenance of a state of alert. However, the potential role played by the orexins in there ward process was evident since one of the first publications following its discovery. Sakurai et al., reported that the administration of Orexin A or Orexin B inside the lateral ventricle produced for aging in rats, which is precisely why they were denominated "orexins", given their appetite stimulating effect [14]. The first reporton the possible role of orexins in addictions appeared in 2003, when Georgescu et al., demonstrated that orexigenic neurons participated in opioid withdrawal when finding that orexin-deficient mice presented reduced naloxone-induced morphine withdrawal symptoms [32]. This was later confirmed by Sharf et al., in 2008 by demonstrating that the selective block age of the Orexin 1 receptor with SB334867 prior to naloxone administration significantly reduced withdrawal symptoms [33]**.** This and other subsequent findings drove various research groups to assess the possible role of this new system of neuropeptides in there inforcement and substance abuse [34]. This function of the orexins associated with reinforcement may be different to their recognized role in the maintenance of a state of alert and is possibly mediated by a different subpopulation of orexigenic neurons in the lateral hypothalamus [35,36].

A global view of the addiction neurocircuits

Although drug abuse frequently produces differential behaviorsand presents different pharmacological profiles, a common characteristic that they share is increased dopaminergic mesolimbic activity in acute phases of the addictive process [37]. This circuit, which has been extensively implicated in the reinforcement properties of natural cues (food or sex) and drugs of abuse, consists indopaminergic projections (DA) from cell bodies in the Ventral Tegmental Area (VTA) towards the limbic structures (amygdala, ventral pallidum, hippocampus, and nucleus accumbens) and cortical areas (Prefrontal Cortex (PFC), Orbitofrontal Cortex (OFC), and anterior cingulate) [38]. These circuits work in parallel, but play different roles in the addictive process [39]. For example, while the Nucleus Accumbens (NAcc) [39] and the ventral pallidum appear to be implicated in the primary reinforcing effects of drugs of abuse [40]; the amygdala, and the ventral and dorsal hippocampus [41], play an important role in the conditioned learning implicated in the addiction process mediating associations with reinforcing cues, which can be particularly important for contextual learningin the addictive process [42].

On the other hand, the PFC, OFC and anterior cingulate regulate the emotional responses, cognitive control, and executive functions [43], in relation to repeated exposure to the drug, leading to cellular adaptations of the glutamatergic pathway that goes from the PFC to the NAcc contributing to the persistence of addictive behaviors [44],

including the reduction of cognitive controland exaggerated responses to drug-associated cues [45]. As mentioned previously, the recurrence of the drug-seeking and substance use behavior following long periods of abstinence, constitute one of the most important problems in relation to the long term treatment of drug addicts [46]. A significant number of factors have been associated to craving (inordinate desirefor drug use, anxiety ortendency) and relapse, such as exposure to environmental cues previously associated with drug use, negative moods or stress [47-49]**.** The study of such factors is one of today's tasks for psychiatry and neuroscience, in order to advance knowledge on the disorder and improve treatment response.

The role of orexins in addictions

The orexigenic LH neurons are anatomically related to regions such as the NAc and VTA, which form part of the cerebral reward systems related to drug addiction [50]. It therefore makes sense to think that such neuropeptides play a role in the addiction process.

The animal models that allow an approximation to the symptoms of human addiction have been crucial to our understanding of the neurobiological mechanisms of PAS addiction [51]. These animal models also offer the possibility to assess new therapeutic strategies for the treatment of addictions [52]. To study the role of orexinsin the addictive process, researchers have chosen to do so through these experimental models (paradigms) that are broadly used to shed light on the neurobiological mechanisms underlying addictive behavior. The experimental models are as follows:

- Self-administration/extinction/reinstatement;
- Conditioned place preference;
- Locomotor activity.

Self-administration: Drug self administration is an animal model widely used in preclinical research into PAS addiction [53]. Among the different animal models, this one best stimulates the condition of addictionin humans [54,55]. The procedure consists in the implantation of a catheter in an animal's jugular vein, and, following recovery, the animal self administers a drug intravenously according to the protocol of the operative conditioning usually by pressing a lever or rummaging with the nose [56]. Drug infusion usually coincides with sound or light cues that facilitate drug acquisition and acquires the properties of conditioned cues. Self-administrationis generally divided into two phases: Acquisition and maintenance [55]. Although there are many variations to the technique, the most commonly used model for relapse following self-administration is the extinction-reinstatement paradigm [54,55]**.** In this model, once self-administration has been established and maintained, the animals are subjected to a process of response extinction, which means that the drug is discontinued, suppressing the animal's drug-seeking behavior [54]. Once the drug-seeking behavioris extinguished, its reinstatement can be triggered by priming injections of the drug, a cue previously associated to the drug, orby aphysical (electric shocks on the paws) or chemical (yohimbine) stressors [57]. Reinstatement following extinction implies the restoration of a concrete operational response, suggesting that this animal model is relevant to understanding relapse in humans [58].

Self-administration and orexins: Orexin 1 infusion into the VTA increased the effects of cocaine and the tonic and phasic signaling of dopamine and increased motivation for the self-administration of cocaine in progressive testing protocol [59]. Similarly, Orexin A receptor knockout mice presented much lower levels of cocaineself-administration than wild-type mice [60].

A number of studies have assessed the role of the orexinergic system in the acquisition and maintenance of drug self-administration. For cocaineself-administration, Orexin 1 Receptor (OX1R) mediated signaling regulates the ingestion of cocaine depending on the reinforcement protocol. For example, in a Fixed Rate Protocol (FR1), acute systemic administration of the Orexin 1 receptor antagonist (SB-334867) or intra-VTA Orexin A (OXA) administration did not affect cocaine self-administration [59,61]. In addition, chronic treatment with SB-334867 (10mg/kg/day) did not affect theacquisition or maintenance of self-administration under the same FR1 protocol [62]. However, when the rats were assessed using a Progressive Rate Protocol (PR), OX1R blockade by means of systemic administration of SB-334867 (10mg/kg/day) significantly reduced cocaine self-administration, indicating reduced levels of drug-seeking [63-65]. In addition, the intra-VTA administration of SB-334867 reduced OXA cocaine self-administration [66], where as the intra-VTA administration increased it [59,63]. Given that the cut-off point for self-administration may reflect the cut-off point for the animal's motivation to access the drug, these data indicate the importance of the orexinergic systemin this aspect, and that high levels of motivation are needed for consumption. In fact, the lack of effect of SB-334867 on cocaine self-administration under a FR1 protocol suggests that the signals measured by OX1R may not be necessary for cocaine ingestion under conditions of low motivation. This is supported by the observation that SB-334867 induced a dose-dependent decrease of cocaine self-administration under a high demand FR5 protocol [64]. Although OXR1 is implicated to a greater extent than OXR2 in the regulation of dopaminergic signals and cocaine self-administration, a recent study showed that the blockade of both types of receptors significantly reduced the effect of cocaineon dopaminergic signaling and the motivation to consume cocaine [67].

On the other hand, under a FR protocol, a reduction of ethanol [68,69] and nicotine [27], self-administration was observed with SB-334867 as well as an increase in the self-administration of these two substances following intracranial application of OXA [26,70]. More specifically, OXA infusion in NAcc showed a significant dose-dependent increase in alcoholingestion in Wistarrats [71].

Similarly, systemic SB-334867 injections significantly reduced the cut-off points for the self-administration of ethanol and nicotine under a PR protocol [26,69]. This finding has been correlated to the fact that OXA microinjections in the lateral hypothalamus and the Paraventricular Nucleus (PVN) increased alcohol ingestion [72]**.** Recent experiments showed that OXR1 blockade reduces alcohol ingestion [73] and that OXR2 blockade with LSN2424100 and the dual antagonism of OX receptors with Alomerxant reduces alcohol ingestion inrats [74]. Other experiments with rats showed that Intracerebroventricular (ICV) administration of the selective antagonist OXR2 TCS-OX2-29 reduced ethanol self-administration but not sucrose self-administration, and it had no impacton the reinstatement of cue-induced alcohol-seeking behaviors. Furthermore,TCS-OX2-29 microinjections in core NAc core reduced ethanol response, indicating that OXR2 in the NAc can mediate the reinforcing effects of ethanol [75]. Complementarily, the intraperitoneal administration of SB334867 [76], in the prelimbic cortex [77], showed a dose-dependent

decrease in the cue-induced reinstatement of ethanol. In the same way as with cocaine, these data suggest that both ingestion and motivation for ethanol [78,79] and nicotine [26], self-administration are regulated by theorexinergic system [65].

Extinction: On the first day of extinction, the animals typically exhibit explosive activity, with behavioral responses to the same level or higher than those observed during self-administration [80]**.** The elevated responses can be interpreted as drug-seeking behavior triggered by contexts associated to the drug, despite the lack of its availability or associated cues [81,82]**.** In rats previously trained for cocaine self-administration, acute pre treatment with SB-334867 on the first day of extinction reduced the explosive resulton that day. However, this effect was only observed during the day of the treatment, given that the response to the extinction was similar to that of the animals in the control groups in the following sessions [83]. Sensitivity to the treatment with SB-334867 also depends on the duration of forced withdrawal. Thus, following a day of withdrawal, only a high dose (30mg/kg) of SB-334867 effectively reduced the context-induced cocaine-seeking behavior. With more protracted withdrawal (14days) or with the extinction of cocaine-seeking behavior in an environment different fromthe context of self-administration, even lower doses (10 and 20mg/kg) of SB-334867 were effective [83]. These changes indicate that the orexinergic system may be involved in drug-seeking behavior following long periods of withdrawal as the increased cocaine seeking behavior during withdrawal showed significant sensitivity to OX1R antagonism. On the other hand, chronic effects of SB-334867 have been reported during extinction. In this sense, Zhou et al., showed that systemic daily injections of SB-334867 prior to each extinction test facilitates the extinction process and attenuates the cocaine-seeking response though extinction sessions [84].

Reinstatement: Following extinction, the direct activation of the orexinergic system may bring about the reinstatement of a previously extinguished response. In fact, ICV or intra-VTA administration of OXA reinstates cocaine-seeking behavior extinguished in animals with a history of self-administration [85,86]. SB-334867 administration produced a dose-dependent attenuation of the cue-induced reinstatement, but it could not affect cocaine priming-induced reinstatement [61]. In addition, treatment with SB-334867 before a simple Pavlovian conditioning session, during which the cues were passively conditioned with cocaine infusions, did not suppress cue-induced reinstatement of extinguished cocaine seeking response [61]. These results suggest that OX1R mediated signalingis not necessary during the acquisition of cue-related associations, but rather during recovery and expression of cue learning [87]. In this sense, Mahler et al., examined whether orexins and glutamate interact within the VTA to promote the reinstatement of cocaine-seeking behavior in a self-administration protocol. They found that bilateral microinjections of the OXR1R SB334867 antagonist or a mixture of AMPA and NMDA receptor antagonists called CNQX/AP-5 reduced the reinstatement of cue-induced cocaine seeking. In contrast, neither the microinjections nor the systemic administration of SB334867 diminished cocaine-precipitated reinstatement. Also, OX1R blockade combined with contralateral VTA glutamate blockade reducedcue-induced reinstatement, indicating that VTA orexin and glutamateare simultaneously necessary for cue-induced reinstatement.

The fact that the orexinergic systemis involved incue-induced reinstatement and not in cocaine-induced reinstatement, indicates that orexin signaling mediates cue-drug associative learning, but not necessarily the primary reinforcing effects of the drug itself such as cocaine-induced reinstatement. Stress-induced reinstatementis also mediated by the orexin system, and this is supported by the observation that SB-334867 causes dose-dependent blockade of electric shock stress-mediated cocaine-seeking [85]. However, this process seems to be independent of VTA signaling, given that intra VTA SB 334867 did not block theelectric shock stress-induced reinstatement [86]. It has been found that the systemic administration of SB-334867 reduced yohimbine chemical stress-induced cocaine-seeking reinstatement [11].

What could explain the difference between the effects of SB on cocaine-seeking reinstatement orits cue-induced self-administration vs. cocaine-induced self-administration? A possible explanation could be that the DA release following morphine administration requires VTA activation, whereas DA release following cocaine use does not [88].

As with other drugs, alcohol intake cue-induced alcohol-seeking reinstatement was reduced through treatment with SB-334867 both immediately and following extinction or protracted withdrawal, which is a model that best simulates alcoholism in humans [70,89,90]. Further more, during reinstatement, alcohol associated cues increased immediate early genes such as Fos in various regions of the brain, including the orexinergic neurons in the Lateral Hypothalamus (LH), and the degree of alcohol-seeking was positively correlated with Fos expressionin the Lateral Hypothalamus (LH) [90-92]**.** SB-334867 also reduced yohimbine stress-induced alcohol-seeking [70,89]. With regards nicotine-administration, ICV infusion of OXA produced seeking-behavior reinstatement [93], an effect that was blocked by treatment with SB-334867 [94]. However, SB-334867 did not blockshock-induced reinstatement [93]. It is possible that the reinstatement of stress-induced nicotine seeking acts through a mechanism that is independent of OX1R activity. However, to prove this, we would require a more complete dose-response study, given that to assess nicotine-seeking only low doses of SB-334867 (5 and 10mg/kg) were used and it has been observed that to attenuate cocaine-seeking reinstatement, doses of 30mg/kg are required [85]**.** The study also showed an attenuation of the signs of nicotine withdrawal inorexin knockoutmice and wild-type mice pretreated with SB334867 [95].

Conditioned place preference: Conditioned Place Preference (CPP) is an animal model widely used to measure the reinforcing effects of drugs of abuse [96-99]. CPP refers to the development of preference foran environment previously associated with non-contingent substance administration [100]**.** In this model, the animal is given an injection of the drug and is then restricted to the side of the chamber with visual and tactile cues which are different to those on the other side of the chamber, accessible only following placebo administration [101]. Subsequently, in drug-free conditions, the animal is allowed to access both sides of the chamber. An increase in the amount of time spent on the side associated with the substance is an indication of a positive reinforcing effect of the drug [102]. With regards the orexin system, the CPP has been used primarily to assess orexin mediation in morphine CPP. The acquisition of morphine CPP was associated with increased activity of the orexinergic neurons in the lateralhy pothalamus, determined by increased Fos expression [103]**.** Thus, bilateral excitotoxic lesions of the LH blocked the acquisition of morphine CPP, and the combination of unilateral excitotoxic lesions of the LH by administration of intra-VTASB-334867 in the contralateral side

also blocked the development of Morphine CPP [104]. Interestingly, the percentage of Fos positive orexinergic neurons revealed a positive correlation with the amount of time spent by the animal in the morphine-associated chamber [104]**.** Thus, the morphine-, cocaine-, or food-conditioned rats showed a substantial increase of c-Fos expression in LH neurons. Both systemic and intra-VTA administration of SB-334867 reduced morphine CPP expression [104-106] and the reinstatement of morphine CPP mediated by the administration of the pancreatic polypeptide in LH was blocked by thesystemic SB-334867 administration [104]**.**

Interestingly, Richardson and Aston-Jones observed that the orexin neuronsthat project to the VTA display Fos activation with morphine CPP, and this activation increases as morphine abstinence in ratsprotracts, indicating that VTA is a possible site for orexinaction in the reinstatement of preference during protracted morphine withdrawal [107]. This phenomenon was limited to orexinneurons in LH and not to neurons in the perifornical area or the dorsomedial hypothalamus.

More recent works have found that the administration of both orexin receptors antagonists SB334867 and TCSOX229 in the NAcc shell significantly reduced stress-induced reinstatement of morphine CPP, but none of the orexin antagonists had an effect on the reinstatement of morphine-induced CPP. These findings indicate that the NAcc shell is an area of the brain through which orexins participate in relapse into stress-induced but not drug-induced morphine-consumption [108,109]**.** It was also observed that the administration of orexin receptor 1 (SB334867) and 2 (TCS OX2 29) antagonists within the dentate gyrus of the hippocampus in rats reduced the reinstatement of drug-induced dose-dependent morphine-seeking but there was no impacton stress-induced reinstatement [110].

As a whole, these data point out the importance of the orexinergic neuronsin the LH and their projections to VTA and NAcc in the development and expression of morphine CPP. Normal preference for the side associated with morphine was observed in animals with neurotoxic lesions outside the LH or in which the counter lateral microinjection of orexin receptor antagonist was applied outside the VTA.

Recent studies have identified a new role for the orexinergic systemin opioid addiction by observing that intra-VTASB334867 administration in rats blocked increased morphine-induced plasticity indopaminergic neurons through the abolishment of an increased rate of glutamatergic receptors AMPA/NMDA, the blockade of increased glutamate release, and inhibition of a change in the number or function of postsynaptic AMPA receptors [111]. These findings constitute a new role for orexins in morphine-induced plasticity in VTA and they provide a mechanism through which orexins can regulate the output of dopaminergic neurons.

These results indicate that the orexinergic neurons in LH are involved in both the conditioned reinforcement process, and in plasticity inVTA associated to the stimulus-response learning of the relationships between the stimulus and the drug [105].

For amphetamine CPP, it has been observed that high doses (30mg/kg) of SB-334867 blocked CPP expression. Interestingly, in contrast to amphetamines and morphine, SB-334867 did not reduce the expression of cocaine-induced place preference [106].

In subsequent experiments with rats, Sartor and Aston-Jones demonstrated thatsystemic administration of SB334867 reduced cocaine-induced CPP, and that the lateral septum neuronsactivate the orexigenic neurons of the LH during cocaine-induced CPP suggesting that this circuit is essential for cocaine-induced CPP [112]. It has also been found that the orexin Messenger RNA levels diminish during CPP in Sprague-Daley (SD) rats [113]. In contrast, in experiments using SD rats, acute cocaine withdrawal provoked increased levels of orexin Messenger RNA in the LH [113]. These results suggest that orexin gene expression in LH is region specific after CPP in SD rats and that increased orexin-gene expression in LH inrats may contribute to the negative emotional states associated to cocaine withdrawal.

Similarly, the acquisition ofethanol CPP was not affected by OX1R blockade with SB-334867 [114]. These differential results for different types of drugs suggest that the reinforcing effects mediated by the orexin systemmay depend on the unique pharmacological profiles of drugs of abuse and on the fact that non-orexigenic neurotransmission systems may be enough for the acquisition and expression of CPP.

Locomotion: Hyper-locomotion and drug-induced behavioral sensitization are measures that are widely used to asses the effects of acute and repeated drug abuse [115-117]. Drug-Induced Hyper-Locomotion (DIHL) refers to the increased motor activity in the animal following acute drug administration [115-117]**.** The animals that show the highest initial locomotion response may be more susceptible to developing compulsive drug self-administration [118,119]. In addition, behavioral sensitization may facilitate the acquisition of self-administration or CPP [120-122]. However, while sensitization has been associated to reinstatement of cocaine-seeking behavior, there have been reports of disassociations between the sensitization and reinstatement of cocaine-induced CPP [118,123]. To date, the studies on the role of the orexinergic systemin DIHL and sensitization are quite limited. In mice with no history of drug consumption, the systemic administration of SB-334867 (10mg/kg) did not affect theirhyper-locomotion induced by acute systemic administration of cocaine at 15mg/kg doses [124]. When a small dose of cocaine was used (10mg/kg), the cocaine-induced hyper-locomotion was blocked by SB-334867 in the three doses usually used (10,20 and 30mg/kg) [84]. However, inrats with a history of cocaine self-administration, even the high dose of SB334867 (30mg/kg) only had a moderate effect on reducing cocaine- induced activity measured by horizontal distance, but it did not affect the total distance covered [61]. For cocaine-induced behavioral sensitization, it was shown that a chronic injection of SB-334867 (10mg/kg) blocks the developments but not the expression of cocaine sensitization [124].

As with other drugs, ethanol-induced hyper activity was attenuated in a dose-dependent manner by pre-treatment with SB-334867 [114]. In this same direction, Macedo et al., observe that chronic ethanol treatment produced behavioral sensitization and increased the number of Fos-immunoreactive orexigenic neurons in mice and that pretreatment with SB334867 blocked the expression of sensitization in mice chronically treated with ethanol [125].

Intracranial infusion of SB-334867 did not affect morphine induced hyper-locomotion activity in the same way as a 30mg/kg dose of SB-334867 did not affect the development or the expression of behavioral sensitization [106,126]. However, acute administration of SB-334867 (30mg/kg) reduced the expression of sensitization to

amphetamines following a period of withdrawal [127]. It has also been shown that SB-334867 reduced dopaminergic reference to NAcc shell evoked by the administration of amphetamine [127] and the activation of orexigenic neuronsin hypothalamic regions increased duringthe amphetamine-induced sensitization [128]. Similarly, the Dual Orexin Receptor Antagonist (DORA) impeded amphetamine-induced behavioral sensitization [129].

All of these findings contribute evidence that allows us to state that the orexin projections of LH to VTA play an important rolein the expression of drug preference, and may also be involved in the recurrence of drug-seeking following withdrawal, which opens possible therapeutic paths in considering thatthe design of medicines that modulatethe orexinergic systemmay provide an alternative to prevent-relapse in patients with substance use disorders in rehabilitation [82].

Discussion

Therapeutic implications

Knowledge of the orexin system may be key in explaining the frequently observed relapse in drug addicts following a period of withdrawal, as the exogenous stimulation of orexin neurons in animals reinstates previously extinguished drug-seeking behavior [85,104]. SB-334867-A administration impedes this recovery of drug-seeking behavior in the presence of cues or contexts that were associated with cocaine or heroin, but it does not affect relapse induced by the drug it self [34,130]. These findings provide a scientific base from which to consider OX1R receptors as potential pharmacological targets in the treatment of relapse in alcohol, morphine, or nicotine addiction [130,131].

Orexin SB334867 antagonist administration does not block cocaine seekinginduced by cocaine itself. This contrasts with the ability of SB334867 to block environmental cue-induced cocaine seeking. One of the most significant consequences of the studies is that selective orexin receptor antagonists maybe used as therapy to prevent relapse and compulsive drug-seeking behavior [132].

If orexin signaling pathway spromote craving, then the use of antagonists of one or both orexin receptors should reduce substance craving and relapseinclinical practice. However orexin antagonists that are currently being developed address mainly sleep disorders and although their kinetics may not be optimal in the treatment of addiction, there are some promising findings. For example, Almorexant, the first Dual Orexin Receptorant Agonist (DORA) [133], reduces CPP for cocaine and amphetamines [134]. Almorexant also reduces alcohol consumption in mice and rats indifferent animal models [74].

However, Simple Orexin Receptor Antagonists (SORA) for orexin 1 [135,136] and orexin 2 receptors [137,138] appear to be more promising in the treatment of addictive disorders [76,78,139,140]. In fact, in preclinical tests with animal models, the pharmacological antagonism of OX1R reduces opioid, psychostimulant, alcohol, and cannabinoid relapse behavior. Similarly, OX2R antagonism has also been shown to reduce opioid and alcohol self-administration [7].

Future directions and problems to solve

Many studies are basedon the use of SB334867 to assess the contribution of OXR1 mediated signals. However, this antagonist shows poor solubility and may also be limited because of its selectivity; thus, the use of local injections virally-mediated with knockout strategies for direct manipulation of OXR1 should be explored [141]. Future studies that examine the effects of orexin projections on VTA or other semipro regions implicated in the motivates conduct may use optogenetic technology to selectively activate or inactivate these projections in atemporarily controlled manner [142]. Some studies reveal a lack of rigorously validated antibodies for the determination of orexins and their receptors. Collaborative efforts are required to establish a gold standard for the quantitative determination of the peptide [143].

A significant number of new orexin receptor antagonists are being prepared, and it is expected that more ligands will be developed soon to be used in research, as will the first medication approved for use against addictive disorders as has already been achieved for insomnia with the DORA Suvorexant [144]. However, bearing in mind the many interactions of the orexinergic systems with other neuropeptide systems, it is worth asking: What could the collateral effectsof these medications be along with their possible new indications? (Table 1).

Reinforcer	Experiment	Observation
Cocaina-Anphetamine	Self-Administration (SA)	Systemic administration of SB334867 reduced lever pressing for cocaine reward [59,62]
		Systemic intra VTA administration of SB334867 reduced cocaine-induced SA [63,65]
		OXR1 (SB334867) and OXR2 (Almorexant) blockade reduced the dopaminergic signaling and cocaine-induced SA [67]
		VTA infusion of OXA promotes cocaine-induced SA in discreet trial and progressive ratio protocol [59]
		OXA knockout miceshowed lower cocaine SA then wild-type mice [60]
		ICV administration of OXA did not alter cocaine-induced SA in rats [61,85]
	Conditioned Place Preference (CPP)	Systemic administration of SB334867 reduced cocaine-induced CPP in rats [112]
		The activation of orexinergic neurons or OXA administration inVTA reinstated reinforcement seeking in a CPP paradigm [104]
		Treatment with SB-334867 reduced context-provoked cocaine-seeking in rats [83]
	Reinstatement	ICV administration deOXA reinstates cocaine-seekingin operative conditioning paradigm [85,86]
		OX1R (SB334867) blockade combined with contralateral glutamate blockade in VTA reduced signal-induced cocaine reinstatement [87]
		SB334867 had no effect on SA established for cocaine,but reduced cocaine-seeking during extinction [84]
	Sensitization	Chronic administration of SB-334867 impeded cocaine-induced behavioral sensitization [124] and SB-334867 reduced amphetamine-induced behavioral sensitization [127]

		SB-334867 reduced amphetamine-induced behavioral sensitization [127]
		A dual orexin receptor-1 antagonist (DORA-1) impeded amphetamine-induced behavioral sensitization [129]
Ethanol	Self-Administration (SA)	ICV administration of selective OXR2 antagonist (TCS-OX2-29) reduced ethanol-induced SAin rats [75]
		OXR1 antagonism with SB334867, OXR2 with LSN2424100, and OXR dual antagonism with Alomerxant reduced alcohol-ingestion in rats [74]
		OXA infusion in NAccshowed a significant increase of dose-dependent alcohol-ingestion in rats [71]
		SB334867 administration reduces ethanol SA in rats [69,70,89]
	Conditioned Place Preference (CPP)	OXR2 (JNJ-10397049) blockade attenuates la acquisition, expression, and reinstatement of ethanol-induced CPP [79]
		SB334867 reduces ethanol-provoked activity without altering ethanol-induced acquisition or expression of CPP in mice [114]
	Reinstatement	Intracerebral and systemic administration of SB334867 in rats, showed dose-dependent decrease of cue-induced reinstatement of ethanol [76,77]
		ICV TCS-OX2-29 administration did not alter cue-induced reinstatement of alcohol-seeking [75]
	Sensitization	Systemic administration de JNJ-10397049 reduce ethanol SA in rats [79]
		Large number of Fos positive hypothalamic orexinergic neuronsin correlation with contextual cue-associated alcohol availability [91]
		SB334867 significantly reduces there in statement of yohimbine-induced ethanol-seeking in rats [89]
		Systemic administration of SB334867 reduces ethanol preference and consumptionin rats [78]
		OXA microinjections in LH and PVN increase ethanol ingestion [68,72]
		Pretreatmentwith SB334867 blocked expression of sensitizationin micechronically treated with ethanol [125]
Morphine/Heroin	Withdrawal	OXR1 (SB334867) blockade before naloxone administration attenuates withdrawal symptoms [33]
		OX deficient mice showed a reduction in signs of naloxone-precipited morphine withdrawal [32]
	Self-Administration (SA)	OXR (SB 334867) blockade reduced cocaine SA and (context) cue-induced morphine seeking [130]
	Conditioned Place Preference (CPP)	SB334867or TCSOX229 administration in NAcc shell reduced reinstatement of stress-induced morphine CPP, but not morphine-induced CPP [108]
		Systemic intra-VTASB-334867 administration reduced expression of morphine-induced CPP [106]
		OXR1 knockout mice showed nomorphine-induced (CPP) intra VTA infusion of SB334867 altered CPP in rats [105]
	Sensitization	OXA microinjections in PVT inhibited morphine-induced locomotion activity in rats [126]
		OX knockout mice treated with SB334867 and controls showed similar locomotion activity after morphine-administration [106]
Nicotine	Self-Administration (SA)	Systemic SB334867 administration diminished nicotine SA in mice [26]
		OXR1 (SB334867) blockade reduced the reinstatement of nicotine-seeking in mice [94]
		OXR1 (SB334867) blockade to OXR dual blockade (Almorexant) reduced nicotine SA [27]
	Withdrawal	Somatic signs of nicotine withdraw alareattenuated in knockout and wild-type mice pretreated with SB334867 [95]
	Conditioned Place Preference (CPP)	ICV infusion of OX1 reinstated nicotine-seeking behavior previously extinguished mice [93]

Table 1: Summary of studies on the role of orexinsin addiction to some psychoactive substances.

Conclusion

The orexigenic systemplays an established role in thedrug seeking and rewards processes and is a therapeutic target for future drug therapy in addictive disorders. Orexin Aacts mainly through OXR1 to increase the synaptic efficacy of the dopaminergic VTA neurons promoting dopamine-release [63,65,124,145,146] which is related to seeking behaviors and reinforcing effects of drugs of abuse. The activation of the orexinergic system by stress may introduce neuroadaptative changes, which may lead to increased susceptibility to drug addiction and relapse. Selective OX1R receptor antagonists such as SB-334867-A or GSK1059865 may help maintain withdrawal and reduce relapse in addictive processes. A greater understanding of this system will probably allow us to design efficient therapeutic interventions that prevent relapses in addicts to drugs of abuse. More studies are needed to shed light on the molecular bases through which these medications manipulate the orexinergic system and modify the reward circuits. There should also be upcoming results to studies in preclinal phase aimed at treating addiction especially to cocaine and opioids.

Conflicts of Interest

None to declare.

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