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The Insomnia-Addiction Positive Feedback Loop: Role of the Orexin System

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Abstract

Significant sleep impairments often accompany substance use disorders (SUDs). Sleep disturbances in SUD patients are associated with poor clinical outcomes and treatment adherence, emphasizing the importance of normalizing sleep when treating SUDs. Orexins (hypocretins) are neuropeptides exclusively produced by neurons in the posterior hypothalamus that regulate various behavioral and physiological processes, including sleep-wakefulness and motivated drug taking. Given its dual role in sleep and addiction, the orexin system represents a promising therapeutic target for treating SUDs and their comorbid sleep deficits. Here, we review the literature on the role of the orexin system in sleep and drug addiction and discuss the therapeutic potential of orexin receptor antagonists for SUDs. We argue that orexin receptor antagonists may be effective therapeutics for treating addiction because they target orexin's regulation of sleep (top-down) and motivation (bottom-up) pathways.

Introduction

Emerging evidence demonstrates that individuals suffering from substance use disorders (SUDs) report significant sleep impairments, including insomnia [1–3]. Indeed, an estimated 70% of patients entering detoxification treatment complain of sleep issues [4], and those

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Author Contributions

All authors were involved in the development and review of the chapter, approved the final version to be published, and take responsibility for all aspects of the work.

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who report issues are at increased risk for relapse [5]. Individuals with SUDs also report using drugs to improve sleep quality [4, 6, 7], further emphasizing the importance of treating sleep disturbances in SUD patients.

There is significant interest in the hypothalamic orexin (hypocretin) system as a potential novel target for medications designed to treat SUDs. Indeed, in 2019, the National Institute of Drug Abuse added orexin receptor (OxR) antagonists to their list of most-wanted medications for the treatment of opioid addiction [8]. Although this interest is largely driven by preclinical studies indicating that orexin neurons are critically involved in translating motivational states into action (i.e., bottom-up processes) [9], we argue that blockade of this system may also reduce drug craving via improvement of sleep outcomes and executive functioning in SUD patients (i.e., “top-down” processes). Here, we outline the most up-to-date evidence implicating the orexin system in these two separate addiction mechanisms. Notably, we provide only a brief overview of the orexin system in sleep and wakefulness, as this topic is described in detail elsewhere in this volume.

The Role of the Orexin System in Sleep and Wakefulness

Orexin-A and orexin-B (also known as hypocretin-1 and hypocretin-2) are neuropeptides exclusively produced by neurons in the posterior hypothalamus that regulate a wide range of behaviors by directly acting on two G-coupled protein receptors, orexin-1 (OX₁R) and orexin-2 (OX₂R) receptors [10]. Orexins were initially recognized as modulators of sleep-wakefulness after the demonstration that narcoleptic dogs have a mutation in the OX₂R [11], and that orexin knockout mice exhibited signs of the sleep disorder narcolepsy [12]. These results were extended by subsequent studies demonstrating that human narcoleptics expressed fewer orexin neurons than healthy controls [13]. Treatments that increase orexin peptide expression (e.g., chronic morphine) have been shown to reverse signs of narcolepsy in orexin-deficient mice [14], further demonstrating a role for orexin in sleep-wakefulness.

Orexins primarily signal wakefulness through the OX₂R. Mice lacking the OX₂R gene exhibit signs of narcolepsy [15] and an OX₂R antagonist promotes sleep in mice and humans [16]. Likewise, mutations of the OX₂R gene contributes to canine narcolepsy [11]. In line with these data, several OXR antagonists (either OX₂R selective or dual) are the subject of ongoing clinical trials for the treatment of insomnia.

The Role of the Orexin System in Drug Motivation

Our laboratory was the first to implicate the orexin system in drug reward, showing that lateral hypothalamic (LH) orexin neurons in rats were Fos-activated in proportion to morphine preference in a conditioned place preference (CPP) paradigm [17]. We also found that stimulation of LH orexin neurons reinstated extinguished morphine CPP, and that this effect was blocked by the selective OX₁R antagonist SB-334867 [17]. Since then, OX₁R antagonists have been shown to attenuate addiction-like behaviors across most drugs of abuse, including alcohol, cocaine, opioids, and nicotine (for review see [9]).

An increase in orexin cell number and activity occurs during paradigms that increase addiction behavior [18–20]. For example, orexin mRNA (detected via *in situ* hybridization) is increased in alcohol-preferring rats following chronic exposure to alcohol [19]. We found

that self-administration paradigms that increase motivation for cocaine or fentanyl in rats are associated with greater numbers of orexin-expressing neurons detected by immunohistochemistry (IHC) [20, 21]. Increased orexin expression is also seen with other opioids; for example, orexin protein levels are increased in mice chronically given morphine and in the postmortem brain tissue of heroin addicts [14].

The role of the orexin system in addiction is not limited to drug taking. Orexins have also been shown to regulate drug withdrawal behaviors, particularly with respect to opioid withdrawal. In rodents, morphine withdrawal increased orexin gene transcription as well as the activity of orexin neurons (indicated by IHC detection of Fos) [15]. Physical signs of morphine withdrawal were attenuated in orexin knockout mice [15] and by OX₁R antagonism [22, 23]. In addition, OX₁R antagonism has been shown to reduce withdrawal-induced increases in Fos expression in several brain areas [22, 23].

Importantly in the context of drug-seeking, the orexin system also plays a role in stress regulation. Stress is a major contributing factor to the development and maintenance of SUDs [24–26], and stress relief is a common cause of initial substance misuse in healthy individuals [27]. In animals, stress facilitates the acquisition of drug self-administration [28], craving [29], and reinstatement of extinguished drug-seeking [26]. Orexins play a critical role in modulating behavioral and physiological responses to stress, particularly concerning stress-elicited drug-seeking. For example, compounds that block orexin signaling are highly effective at reducing stress-elicited seeking of opioids [30], stimulants [31], and alcohol [32]. Given the fundamental role of stress in drug addiction, OXR antagonists may effectively treat SUDs by decreasing relapse associated with stressful life events.

An Addiction-Insomnia Positive Feedback Loop?

The relationships reviewed above among orexin signaling, insomnia, and drug motivation indicate a possible self-reinforcing feedback loop between insomnia and addiction linked by plasticity in orexin neurons (Fig. 1). In this hypothesis, drug use increases orexin expression and signaling, which both interferes with sleep and in parallel drives a hyper-motivated state. Insomnia caused by elevated orexin also degrades executive function which compromises attempts at drug abstinence. Continued drug exposure further increases orexin signaling and the consequent insomnia, hyper-motivation and compromised executive function, creating a vicious cycle that perpetuates the addiction-insomnia problem via orexin hyper-signaling.

In line with this hypothesis, we propose that OXR antagonists might be ideal for breaking this loop. By decreasing orexin signaling, an orexin antagonist can limit insomnia and hyper-motivation, and perhaps also limit the plasticity response in orexin neurons that otherwise increases orexin signaling.

Dual Orexin Antagonists and Selective OX₂R Antagonists Facilitate Sleep/Treat Sleep Dysfunction

Evidence that signaling via the OX₂R promotes waking (as reviewed above) indicates that compounds that block signaling at OX₂Rs might improve sleep. The first wave of such compounds designed to treat sleep dysregulation were developed to block signaling at both

OX₁R and OX₂R, as preclinical studies indicated that better sleep outcomes were achieved with dual versus selective blockade [33]. As of mid-2021, two compounds, suvorexant (Belsomra™, Merck Inc.) and lemborexant (Dayvigo™, Esai Inc.), have received approval from the US Food and Drug Administration (FDA) for the treatment of insomnia. Suvorexant and lemborexant have been shown to improve both objective and subjective sleep measures, including reducing Insomnia Severity Index scores and increasing sleep duration [34, 35]. In addition, both medications have been found to be well-tolerated with minimal side effects. Daridorexant (Idorsia Pharmaceuticals Ltd), another dual orexin antagonist (DORA), showed promise in Phase 3 trials [36] improving night-time sleep and daytime functioning, and its New Drug Application has been submitted to the FDA for review in January 2021. Recently, there has been some interest in the development of selective OX₂R antagonists (2-SORAs), including seltorexant (Minerva NeuroSciences and Janssen Pharmaceuticals), which Phase 2 clinical trials have revealed to improve sleep quality in patients with insomnia alone or comorbid with major depressive disorder [37, 38]; a Phase 3 clinical development program is currently ongoing.

OX₁R Signaling Drives Motivation for Drug Rewards: Implications for Addiction Therapeutics

As discussed above, OX₁R signaling promotes addiction-related behaviors across numerous drugs of abuse [17, 39, 40], indicating that selective OX₁R antagonists (1-SORAs) may be effective in treating SUDs in clinical populations. The orexin system seems to play a universal role in cue-induced reward seeking. Orexin neurons are activated in response to drug-associated cues and contexts [9, 17, 20]. This is consistent with previously published reports showing that the OX₁R is necessary for cue-induced reinstatement of seeking for heroin, remifentanyl, cocaine, ethanol, nicotine, and sucrose [40–44]. Interestingly, our work, and that of others, indicate that 1-SORAs may be particularly useful in treating individuals with the most severe cases of addiction. We showed that OX₁R blockade selectively reduced home-cage ethanol drinking and self-administration in high-alcohol-preferring rats [43, 45]. Using a behavioral economics task, we found that the selective OX₁R antagonist SB-334867 preferentially decreased motivation for cocaine and fentanyl in rats with the strongest demand for these drugs [46, 47]. Rats highly motivated for cocaine or fentanyl were also sensitive to lower doses of SB-334867 than rats with a milder addiction phenotype [20, 21, 48]. OX₁R antagonists are generally non-sedating at doses that reduce drug-seeking [20, 47, 49], and thus likely attenuate addiction behaviors by directly attenuating a hyperresponsive orexin motivational system. There are currently no FDA-approved 1-SORAs for clinical use; however, several candidates are in development, e.g., ACT-539313 and JNJ-61393215.

Collectively, this evidence supports the use of DORAs (or 2-SORA) to treat sleep disturbances and 1-SORA to attenuate hyper-motivation. Although there are currently no FDA-approved 1-SORAs, we argue that DORAs represent an attractive therapeutic for SUDs as they are effective in improving sleep and are likely to attenuate addiction behaviors via inhibiting OX₂R and OX₁R signaling, respectively. Indeed, we note that several clinical studies are currently ongoing to determine the efficacy of these compounds for improving both sleep and craving outcomes in SUDs (Table 1). While we applaud these efforts, below

we outline key considerations that should be addressed with respect to the clinical use of DORAs in SUD populations.

Advantages, Limitations, and Future Considerations regarding DORAs as Addiction Therapeutics

Current treatment avenues for individuals with comorbid addiction and sleep disorders are very limited, highlighting the need for alternative therapeutics. Benzodiazepines are rarely used as sleep therapeutics in SUD patients due to their abuse potential and ability to compromise respiration. This is especially important for opioid patients as opioids also decrease respiratory function. Although *prepro-orexin*-knockout mice exhibit attenuated hypercapnic chemoreflexes compared to wild-type animals [50], human studies have demonstrated a diminished hypoxic respiratory response only in narcoleptic patients with the HLA-DQB1*0602 allele [51]. This indicates that the association with compromised respiratory function is more tightly aligned with the specific allele rather than an orexin deficiency. Thus, it is not surprising that, unlike commonly prescribed sedative-hypnotic agents, such as benzodiazepines and the non-benzodiazepine “Z” drugs, DORAs such as FDA-approved suvorexant and lemborexant are not associated with clinically significant adverse respiratory outcomes during sleep [52, 53]. Therefore, DORAs may offer a safer sleep-related respiratory profile, especially for persons taking opioids who are already at risk for sleep-disordered breathing [54]. We note, however, that the effect of DORAs on respiratory outcomes is yet to be examined in patients with opioid use disorder or who are also under opioid substitution therapy; these experiments will be important for determining the suitability of these compounds for this population.

Although animal studies indicate no abuse potential of DORAs such as suvorexant [55], humans with a history of polysubstance abuse report higher “liking” for suvorexant compared to placebo [56]. This finding raises the possibility that a history of drug abuse might increase suvorexant’s abuse liability. Accordingly, suvorexant and lemborexant are designated by the Drug Enforcement Administration (DEA) of the US as Schedule IV-controlled substances; however, we note that further studies are necessary to fully examine the abuse potentials of DORAs, particularly in individuals with a history of substance abuse.

Although DORAs appear to be an attractive therapeutic strategy for addiction, there are several key questions that need to be addressed. A first step is to test the effectiveness of DORAs in attenuating addiction-like behaviors such as drug taking, relapse, craving, and withdrawal in preclinical models across multiple drug classes. To date, only a small number of preclinical studies have tested the efficacy of a DORA on addiction-like behaviors. Two studies in rats indicated that suvorexant reduced the motivational properties of cocaine and improved cocaine-induced deficits in impulsive behavior [57, 58]. We reported that suvorexant decreased motivation for fentanyl on a behavioral economics task, an effect that was greatest in rats with the highest motivation for fentanyl [59]. A preliminary randomized clinical study indicated that suvorexant reduced several relapse-related indices in patients with cocaine use disorder [60]. Although these results are promising, future studies are necessary to further test the efficacy of DORAs for SUDs.

Second, DORA dosing should be optimized to simultaneously maximize its sleep-promoting effects and anti-craving properties. Bedtime dosing of DORAs to induce sleep results in limited bioavailability the following day when the opportunity for drug use is high [61]. We reported that the anti-drug-seeking effects of suvorexant and the selective OX₁R antagonist SB-334867 extend beyond their bioavailability (up to 48 h post-dosing) when administered to rats during the active period [59, 62]; it will be important to test whether this is also the case when given at the onset of the inactive period. An alternative approach might be combining a DORA at bedtime with a selective OX₁R antagonist (such as those in development, described above) in the morning.

The orexin system is important for facilitating a range of motivated behaviors, and thus chronic suppression of orexin signaling might promote a non-motivated or depressive state. Indeed, orexin system function is lower in both rats and patients exhibiting depression-like symptoms [63–65]. Moreover, administration of suvorexant has been linked to the worsening of depression symptoms and onset of suicidal thoughts [66] (but see [67] for antidepressant effects of seltorexant). This risk might be present in SUD given the high comorbidity of depression in these patients [68].

In addition, although clinical studies indicate minimal effects of suvorexant on memory, negative effects have been observed at high doses in elderly populations or when combined with alcohol in healthy adults [69, 70]. We have reported that an OX₁R antagonist had no effect on response inhibition in rats [49], but further characterization of potential effects of DORAs on cognition is needed.

Finally, it is important to consider potential interactive effects of DORAs as an adjunct to conventional opioid management therapies such as buprenorphine. Of note, patients prescribed suvorexant are advised against next-day driving and other activities requiring full alertness as some patients reported daytime somnolence at 9 h post-dosing [71]; it is unclear whether these effects would be exacerbated by concurrent buprenorphine therapy, which in itself can be sedating [72]. Moreover, although suvorexant has not been found to have adverse respiratory effects in clinical trials [53, 73, 74], this has not been tested in the presence of opioids such as buprenorphine that can also have respiratory suppressing effects [75–77].

Although these are relevant considerations, there are reasons to hypothesize that they will not seriously impede the use of DORAs to treat SUDs. Importantly, for each of these considerations, we found that suvorexant and other OxR antagonists are effective at suppressing drug-seeking at lower doses in animals that exhibit a strong addiction phenotype than in animals with more moderate addiction-like behaviors [20, 21, 46, 59]. Thus, the potential deleterious effects outlined here might be circumvented by prescribing lower doses of a DORA than what is required in a non-SUD population; of course, this possibility would need to be tested more thoroughly in both preclinical and clinical studies.

Conclusion

As summarized above, orexin receptor antagonists show promise as a novel treatment for SUDs. Specifically, we propose that DORAs may be effective at treating SUDs by simultaneously suppressing drug craving (“bottom-up” processes) and improving sleep outcomes and executive functioning (“top-down” processes). As we have outlined, there are several important questions that need to be addressed in order to help realize this potential and confirm both the safety and efficacy profile of DORAs in treating addiction.

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Key Take-Home Points

- Sleep impairments are comorbid in individuals with substance abuse disorders.
- There is a positive feedback loop where drug intake causes increased orexin signaling, which in turn increases motivation for drug and impairs sleep and executive function, causing further drug intake.
- Orexin receptor antagonists can break the cycle between drug use, motivation and sleep deficits.

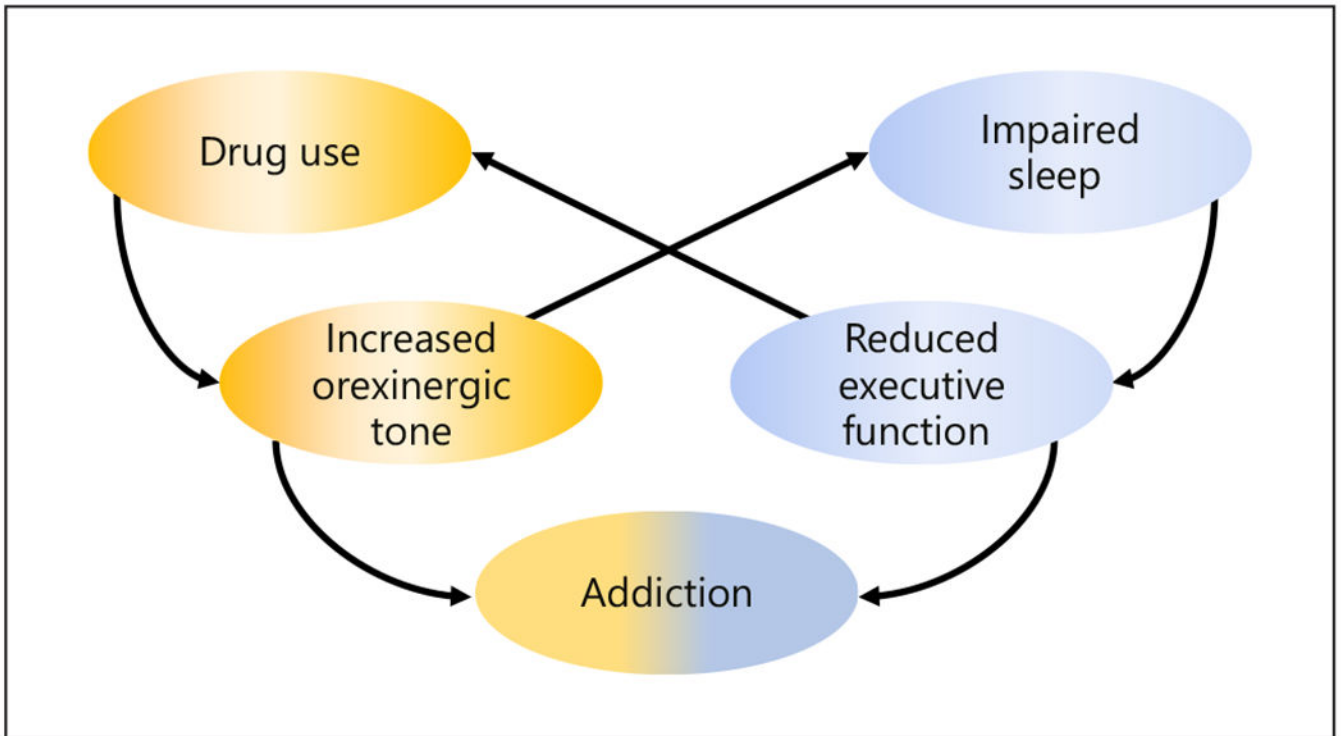


Fig. 1. Schematic illustrating proposed positive feedback loops linking orexin plasticity, insomnia, and addiction.

Table 1.

Clinical trials of orexin receptor antagonists for the treatment of substance abuse disorders

Title of trial	Status	Conditions	ClinicalTrials.gov Identifier
Medication Development in Alcoholism: Suvorexant versus Placebo	Not yet recruiting	Alcohol use disorder	NCT04229095
Suvorexant in the Management Comorbid Sleep Disorder and Alcohol Dependence	Recruiting	Alcohol use disorder	NCT03897062
Suvorexant and Cocaine	Recruiting	Cocaine use disorder	NCT03937986
Role of the Orexin Receptor System in Stress, Sleep and Cocaine Use	Completed	Cocaine use disorder/ Anxiety	NCT02785406
Medical Management of Sleep Disturbance During Opioid Tapering	Recruiting	Opioid use disorder	NCT03789214
Examining the Role of the Orexin System in Sleep and Stress in Persons with Opioid Use Disorder	Recruiting	Opioid use disorder	NCT04287062
Dual-Orexin Antagonism as a Mechanism for Improving Sleep and Drug Abstinence in Opioid Use Disorder	Recruiting	Opioid use disorder	NCT04262193
The Efficacy of Suvorexant in Treatment of Patients with Substance Use Disorder and Insomnia: A Pilot Open Trial	Enrolling by invitation	Opioid use disorder Alcohol use disorder	NCT03412591
Suvorexant to Reduce Symptoms of Nicotine Use	Not yet recruiting	Nicotine dependence	NCT04234997
Targeting Orexin to Treat Nicotine Dependence	Recruiting	Nicotine dependence	NCT03999099

A [ClinicalTrials.gov](#) search (accessed on Jan 1, 2021) yielded ten trials of orexin system modulators for substance use disorders at different stages of progress in the US and Australia, as listed here.