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Research report

The potential role of the orexin reward system in future treatments for opioid drug abuse

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HIGHLIGHTS

- Orexin serves as a bridge between the lateral hypothalamus and the reward system.
- Orexin system has a crucial role in morphine conditioned place preference.
- Orexin antagonists may have a potential therapeutic use in addiction.

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ABSTRACT

Despite a history of more than a century of intense research in drug addiction, with currently available medication and behavioral therapy, the rate of relapse to drug use is 40–60 percent within a year after the cessation of treatment. The discovery of the neuropeptide orexin/hypocretin in 1998 and subsequent research during the past 20 years revealed an important role for the lateral hypothalamus (LH) in driving the reward pathway. The present review includes an overview of the orexinergic system and focuses on the role of LH orexin neurons targeting different components of the brain's reward pathway in addictive behaviors. Among major animal models of drug reinforcement and addictive behaviors, we narrowed our focus to include conditioned place preference (CPP) and self-administration methods. In this regard, studies on both orexin-1 receptors (OX1Rs) and orexin-2 receptors (OX2Rs) have shown some positive results, suggesting that single orexin receptor antagonists (SORAs) and dual orexin receptor antagonists (DORAs) may hold promising efficacy in the treatment of addiction compared to the currently used methods. We conclude that since current evidence is still preliminary, development of new SORA and DORA compounds and their evaluation in animal and clinical studies will guide us in our future efforts for developing effective medication.

1. Clinical aspects of substance use disorders

Substance use disorder is a maladaptive pattern of substance use leading to clinically significant impairment or distress, as defined by the Diagnostic and Statistical Manual of Mental Disorders; Fifth Edition (DSM-5). Clinically, a substance use disorder is diagnosed when two or more of the DSM-5 criteria are present within a 12-month period (Supplementary Table 1). The severity of substance use disorder is measured based on the number of diagnostic criteria met by the patient at the time of diagnosis: 2–3, mild; 4–5, moderate; ≥6, severe (American Psychiatric Association, 2013). Drug addiction is a chronically relapsing disorder, characterized by a compulsion to seek and take the drug, loss of control in limiting drug intake, and the emergence of a negative emotional state like dysphoria, anxiety, and irritability when access to the drug is prevented (Koob and Volkow, 2016). Transition to addiction, moving from impulsivity to compulsivity, is a progression of three consecutive phases: 1) recreational and sporadic drug use, in which drug intake is moderate and occasional; 2) intensified, sustained, and escalated drug use, in which drug intake intensifies frequency and intake amount; and 3) loss of control and full drug addiction, where a

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crystallization of behavior around drug-taking is present and drug-devoted activities are the principal occupations of the individual (Piazza and Deroche-Gamonet, 2013).

2. Current approaches for the treatment of opiates addiction

Traditional treatment of substance use disorders often includes detoxification, aimed at reducing withdrawal symptoms, followed by helping to re-establish normal brain functions and to diminish cravings and prevent relapse (Larsen et al., 2014). For example, medically-supervised withdrawal and maintenance treatment for opiates may include the use of methadone, naltrexone, buprenorphine, and clonidine (National Consensus Development Panel on Effective Medical Treatment of Opiate Addiction, 1998). Methadone, a μ-opioid receptor agonist, has a slow-onset, long duration of action, and once-daily dosing that produces a blunted euphoric effect and may prevent withdrawal symptoms for about 24 h. Naltrexone is a μ-opioid receptor antagonist that blocks the cognitive and behavioral effects of opioids. Buprenorphine is a partial agonist at the μ-opioid receptor that attenuates withdrawal symptoms because of its prolonged occupation of the receptors. Clonidine is an alpha-2 agonist that reduces many of the autonomic signs and symptoms of opioid withdrawal (National Consensus Development Panel on Effective Medical Treatment of Opiate Addiction, 1998). With currently available medication and behavioral therapy for addiction, the rate of relapse to drug use is from 40% to 60% within a year following cessation of treatment (Volkow et al., 2011). Therefore, the treatment of substance use disorders represents a substantial area of unmet medical needs (Fuehrlein and Ross, 2017). In this context, the discovery of the orexin neuropeptide (also called hypocretin) in 1998 and later findings that revealed its role in signaling drug-related reward opened a new horizon in the neurobiology of addiction. As a result, orexin receptors are being considered as a tentative target for developing candidate drugs with strong therapeutic potential for the treatment of opioid use disorder.

The present review aimed to refine our current understanding of how the orexin system is involved in opiates addiction and to discuss the current evidence pointing to the potential efficacy of orexin-based therapies for the treatment of opiates addiction. We also discussed novel opportunities that orexin-based therapies may present.

3. Orexin, the bridge between the lateral hypothalamus and the reward system

The orexin/hypocretin system consists of two types of G-protein coupled receptors: the orexin-1 (OX1Rs) and the orexin-2 (OX2Rs) receptors; and two neuropeptides: orexin-A and orexin-B, both derived from prepro-orexin in the LH by a cascade of enzymatic reactions (Gatfield et al., 2010). Orexin-A is a 33-aminoacid peptide that activates both OX1Rs and OX2Rs with similar potencies, whereas orexin-B is a 28-aminoacid peptide and modestly selective for OX2Rs (Matsuki and Sakurai, 2008). Although the orexin neurons are few in number, the orexin receptors are distributed throughout the central nervous system (CNS). While many brain areas express both OX1Rs and OX2Rs, some regions only express either OX1Rs or OX2Rs (Marcus et al., 2001). The orexin system is conserved across many mammalian species, and a high level of structural and functional homology has been reported between rat and human orexin receptors (Nilaweera et al., 2003). Having extensive projections, the orexin neurons in the LH affect a variety of homeostatic functions (Sakurai et al., 2005; de Lecea and Sutcliffe, 2005; Peyron et al., 1998) including the wakefulness, likely to promote goal-oriented behavior and energy homeostasis (Mileykovskiy et al., 2005; Lee et al., 2005; Chemelli et al., 1999).

The mesocorticolimbic dopaminergic system was, for many years, the center of focus in investigations on drug reward and craving and the related neural changes in reward-sensitive regions (Chen et al., 2010; Deadwyler, 2010). However, in 1954, it was shown that electrical stimulation of the LH induced a profound reinforcement, represented by a robust intracranial self-stimulation (ICSS) in rodents (Olds and Milner, 1954; Olds, 1965). In 1958, Olds declared that a specific motivation system can be found in the LH of rats and subsequently labeled this region as the “pleasure center” (Olds, 1958). Subsequent studies showed that ICSS is more robust in the LH than in other brain regions (Gallistel et al., 1981), and can be modulated by opiates and several other drugs of abuse and their antagonists (Adams et al., 1972; Goodall and Carey, 1975). The medial forebrain bundle (MFB) was shown to be important for overcoming barriers to get a food reward (Morgane et al., 1961). These studies revealed the important role of the LH in reward-seeking behavior.

Georgescu and colleagues showed the involvement of LH orexin neurons in morphine dependence and withdrawal (Georgescu et al., 2003). Other studies indicated that different sets of hypothalamic orexin neurons may have different functions. The orexin neurons in the perifornical area and dorsomedial hypothalamic nucleus regulate arousal, whereas those in the LH regulate reward processing (Mahler et al., 2014; James et al., 2017). There is also a dichotomous role of OX1Rs and OX2Rs in the brain. OX1Rs are mostly implicated in driving drug-seeking for morphine (Harris et al., 2005; Harris, 2007) and cocaine (Harris et al., 2005; Borgland et al., 2006), whereas OX2Rs are implicated largely in sleep/wake cycle regulation and arousal (Willie et al., 2003). Orexin neurons project to the major components of the reward system such as the ventral tegmental area (VTA), nucleus accumbens (NAc), and medial prefrontal cortex (Baldo et al., 2003; Fadel and Deutch, 2002). The mesolimbic dopamine system is a well-recognized target for drugs of abuse, and plasticity within this system has been implicated in the development and maintenance of addiction (Hyman et al., 2006; Kauer and Malenka, 2007). VTA neurons are the main source of dopamine for the ventral striatum and the prefrontal cortex, the critical forebrain regions that mediate incentive learning and reinforcement mechanisms associated with rewards (Berridge, 2007). The VTA receives intense projections from the LH. Indeed, the LH is one of the largest sources of input fibers to the VTA (Phillipson, 1979). Orexin projections form about one-fifth of the inputs (Fadel and Deutch, 2002) and although a major share of the fibers is in close proximity to dendrite and cell bodies of dopamine neurons (Fadel and Deutch, 2002), five percent of them form synapses with GABA-containing neurons (Balcita-Pedicino and Sesack, 2007).

Orexin neurons have been shown to be activated by drugs (Yeoh et al., 2012; Rao et al., 2013) and drug-related cues (Harris et al., 2005). In addition, bilateral neurotoxic lesions that abolished more than fifty percent of LH orexin neurons prevented learning to associate an environment with morphine reward (Harris et al., 2007). Orexin also increased the firing rate of VTA dopamine neurons and enhanced dopamine release in downstream targets (Korotkova et al., 2003; Narita et al., 2006; Narita et al., 2007; Vittoz and Berridge, 2006). The levels of dopamine and its major metabolite in the NAc core were found to be markedly increased by microinjection of orexins into the VTA. These results strongly suggest that activation of orexin-containing terminals in the VTA leads to the direct activation of mesolimbic dopamine neurons at the somatodendritic level (Narita et al., 2006). Indeed, orexin potentiated excitatory synaptic transmission onto the VTA dopamine neurons and promoted drug-seeking behavior (Baimel and Borgland, 2012). In contrast, intra-VTA injection of SB-334867, an OX1R antagonist, attenuated the development and expression of morphine-induced conditioned place preference (CPP) in rats (Sadeghzadeh et al., 2016).

Although, there is still a lack of concrete evidence linking orexin and addiction in human patients, there is compelling evidence that orexin neurons are required for the development of reward-seeking and addiction in both animal models and human patients (Baimel and Borgland, 2012; España and Calipari, 2012; Mahler et al., 2012). Firstly, orexin neurons showed Fos-activation when animals were exposed to opiates, cocaine, amphetamine, and nicotine (Georgescu et al.,

Table 1
Studies investigating the role of orexin receptors 1 (OX1Rs) and orexin receptors 2 (OX2Rs) in different areas of the brain in the acquisition, expression, extinction, and reinstatement phases of morphine conditioned place preference (CPP), morphine dependency (withdrawal), and sensitization.

Phases	Tools	Technique	Main result(s)	Reference
Acquisition phase	In vivo (rats) OX1R antagonist	Conditioned place preference	Bilateral administration of OX1R and OX2R antagonists into the NAc attenuated the acquisition of morphine CPP	(Alizamini et al., 2017)
	In vivo (rats) OX2R antagonist		Bilateral administration of OX1R and OX2R antagonist into the VTA attenuated the acquisition of morphine CPP	(Farahimanesh et al., 2017)
	In vivo (rats) OX2R antagonist		Bilateral administration of OX2R antagonist into the CA1 attenuated the acquisition of morphine CPP	(Sadeghi et al., 2016)
Expression phase	In vivo (rats) OX1R antagonist	Conditioned place preference	Intra-NAc administration of OX1R, but not OX2R, antagonist just before CPP test attenuated the expression of the morphine-induced CPP	(Sadeghzadeh, 2016)
	In vivo (rats) OX2R antagonist		Intra-VTA microinjection of both OX1R and OX2R antagonists significantly attenuated morphine CPP expression	(Farahimanesh et al., 2017)
	In vivo (rats) OX1R antagonist		Intra-CA1 administration of OX1R antagonist attenuated the expression of morphine-induced CPP	(Farahimanesh et al., 2018)
	In vivo (rats) OX2R antagonist		Bilateral administration of OX2R antagonist into the CA1 attenuated the expression of morphine CPP	(Sadeghi et al., 2016)
Extinction phase	In vivo (rats) OX2R antagonist	Conditioned place preference	Bilateral administration of OX2R significantly shortened extinction latency period	(Sadeghi et al., 2016)
	In vivo (rats) OX1R antagonist OX2R antagonist		Intra-NAc administration of the highest dose of OX1R and OX2R antagonists decreased the extinction latency and place preference to morphine-chamber during the extinction phase	(Sadeghzadeh et al., 2016)
	In vivo (rats) OX1R antagonist		Intra-CA1 administration of OX1R antagonist significantly shortened the extinction latency of morphine rewarding properties during the CPP paradigm	(Farahimanesh et al., 2018)
Morphine reinstatement	In vivo (rats) OX1R antagonist OX2R antagonist	Conditioned place preference Forced swim stress (FSS) Western blot	1) Blockade of OX1Rs and OX2Rs in the DG region significantly prevented the morphine priming-induced reinstatement of CPP 2) The FSS-induced reinstatement was slightly attenuated by the blockade of OX1Rs within the DG but OX2Rs antagonist had no effect on the FSS-induced reinstatement	(Ebrahimian et al., 2016)
	In vivo (rats) OX1R antagonist		The significant increase in the phosphorylation of AKT in the DG was associated with preference for the morphine-paired chamber in rats, which was reversed by the local administration of an OX1R antagonist	(Guo et al., 2016)
Morphine withdrawal	In vivo (rats) OX1R antagonist	Plexiglas test chamber	Intra-LC microinjection of orexin-A induced morphine withdrawal-like signs in both morphine-dependent and control rats; Administration of selective OX1R antagonist before orexin-A significantly suppressed orexin-induced morphine withdrawal-like signs	(Ghaemi-Jandabi et al., 2017)
	In vivo (rats) OX1R antagonist Glutamate		Intra-LC microinjection of OX1R antagonist pretreatment did not affect glutamate-induced morphine withdrawal signs during the rest phase; Intra-LC microinjection of OX1R antagonist attenuated glutamate-induced morphine withdrawal-like signs during the active phase	(Hooshmandi et al., 2017)
	In vivo (rats) OX1R antagonist Naloxone		Administration of OX1R antagonist into the LC before each morphine injection significantly decreased somatic signs of naloxone-induced morphine withdrawal syndrome	(Mousavi et al., 2014)
Morphine withdrawal	In vivo (mice) OX1R antagonist Naloxone	Clear plastic home cage C-fos immonohistochemistry	Intraperitoneal injection of OX1R antagonist prior to naloxone-precipitated withdrawal demonstrated a striking reduction in several withdrawal symptoms; Withdrawal was accompanied by an increase in c-Fos expression in the nucleus accumbens shell, which was reduced by OX1R antagonist, but had no effect on the VTA or LC; Morphine withdrawal increased c-Fos expression in the dorsomedial hypothalamus (DMH) and perifornical (PFA) regions but not in the lateral region of the LH (LLH)	(Sharf et al., 2008)
Morphine sensitization	In vivo (mice) OX1R antagonist	Locomotor activity(round actometer cages) Real-time PCR	OX1R antagonist inhibited the acquisition of morphine-induced sensitization to locomotor activity in mice; mRNA expression of OX1Rand OX2R in mice significantly decreased during the acquisition phase of morphine-induced sensitization. OX1R antagonist reversed the reduction; Administration of morphine significantly reduced mRNA expression of both orexin receptors in the hippocampus and prefrontal cortex, but not stratium, showing the involvement of both receptor types in morphine-induced sensitization	(Lupina et al., 2018)

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Table 1 (*continued*)

Phases	Tools	Technique	Main result(s)	Reference
Morphine sensitization	In vivo (rats) OX1R antagonist Cholinergic agonist	Conditioned place preference	Concurrent intra-LH administration of carbachol and an ineffective dose of morphine significantly induced CPP. Additionally, the blockade of OX1R in the VTA attenuated the conditioning score induced by concurrent administration of carbachol and an ineffective dose of morphine	(Razavi et al., 2014)
Morphine sensitization	In vivo (mice Orexin −/−, OKO) OX1R antagonist	Conditioned place preference Locomotor activity	OKO animals displayed normal morphine sensitization. OKO mice did not significantly differ from WT controls in locomotor activity. While OKO mice did not differ from WT controls in preference for a morphine-paired environment, the OX1R antagonist significantly attenuated place preference for morphine in the sensitization phase	(Sharf et al., 2010)

SB334867 and TCS OX2 29, OX1R and OX2R receptors antagonists, respectively; CA1, Cornu Ammonis area; DG, Dentate Gyrus of Hippocampus; HIP, Hippocampus; LC, Locus coeruleus; NAc, Nucleus Accumbens; VTA, Ventral Tegmental Area.

2003; Harris et al., 2005; Pasumarthi and Fadel, 2008; McPherson et al., 2007; Plaza-Zabala, 2012). Secondly, drug-seeking behavior was elicited by the infusion of orexin into the reward-related areas of the brain (Harris et al., 2005; España and Calipari, 2012; Boutrel et al., 2005). Thirdly, drug-seeking behavior was impaired after disruption of orexin receptor-mediated signaling with pharmacological or genetic approaches (Georgescu et al., 2003; Borgland et al., 2006; España and Calipari, 2012; LeSage et al., 2010; Hollander et al., 2012; Hollander et al., 2008). In sum, the research during the past 20 years has revealed an important role for the LH in driving the reward circuitry and has indicated that orexin is the main bridge between the LH and the mesolimbic pathway for reward processing.

4. The role of orexin system in morphine reinforcement

Here, we focused on the involvement of the orexin system in morphine reward and reinforcement using the CPP model. The CPP is one of the most commonly employed paradigms for studying drug-related reward and addiction-like behaviors. In this model, a special context is associated with the rewarding properties of drug. The model has been used to determine how the acquisition and/or expression of the addictive behaviors are affected by experimental manipulations of the orexin system (Harris et al., 2007; Sharf et al., 2010; Farahimanesh et al., 2017).

Harris and colleagues showed that the LH orexin neurons are activated by morphine-context pairing during the acquisition phase of CPP and that systemic administration of an OX1R antagonist, SB-334867, before the drug-free CPP test markedly reduced the expression of morphine-seeking (Harris et al., 2005; Harris et al., 2007). We elaborated on this concept to further elucidate the role of orexin neurons in reward processing. Our results revealed that: 1) Chemical stimulation of the LH by local injection of carbachol, a muscarinic and nicotinic receptor agonist, induced CPP in rats (Taslimi et al., 2011) and potentiated the rewarding properties of a sub-effective dose of morphine (Zarepour et al., 2013). 2) Blockade of OX1Rs in the VTA inhibited the acquisition of both LH stimulation CPP (Taslimi et al., 2011) and LH stimulation-induced potentiation of morphine CPP (Zarepour et al., 2014). 3) Dopaminergic transmission in the NAc was involved in CPP induced by the LH stimulation (Haghparast et al., 2013). 4) Chemical stimulation of the LH changed the phosphorylation rate of CREB and ERK, and c-fos induction in the VTA, hippocampus, and prefrontal cortex after the CPP test, which indicates a functional relationship between the LH and other brain areas involved in reward processing in rats (Haghparast et al., 2011). 5) Orexin receptors in the CA1 region of the hippocampus were critically involved in LH stimulation-induced CPP, as intra-CA1 administration of SB-334867 or TCS-OX2-29 (the OX1R and OX2R antagonists, respectively) significantly attenuated the development of CPP induced by the stimulation of the LH (Rashidy-Pour et al., 2015). 6) Administration of orexin-A into the VTA produced CPP in a dose-dependent manner and blockade of D1 or D2 receptors of the ipsilateral NAc inhibited the effect (Taslimi et al., 2012).

Haghparast and his team further investigated the role of orexin receptors in morphine-seeking. Their findings revealed that both OX1Rs and OX2Rs in the VTA are critical for the acquisition and expression of morphine CPP (Farahimanesh et al., 2017). Additionally, blockade of OX1R, but not OX2R, in the NAc during the CPP test attenuated the expression of morphine-seeking. However, blockade of both receptors decreased the development of morphine CPP and shortened the extinction phase in rats. The latter effects were more significant when OX1Rs were blocked, suggesting that OX1Rs within the NAc are critical for the development, expression, and maintenance of morphine-seeking behaviors (Sadeghzadeh et al., 2016; Alizamini et al., 2017). The team also showed that OX1Rs in the CA1 were involved in the expression and maintenance of morphine-seeking, as intra-CA1 administration of the antagonist attenuated the expression and facilitated the extinction of morphine CPP (Farahimanesh et al., 2018). Moreover, blockade of

OX2Rs in the CA1 attenuated the acquisition and expression of morphine CPP (Sadeghi et al., 2016). Table 1 summarizes the data on the role of orexin receptors in other aspects of morphine use.

5. The role of orexin system in morphine withdrawal syndrome

Opioids produce euphoric effects that favor chronic drug use culminating in dependence (O'Brien, 2011). In contrast, abstinence from opiate use in dependent individuals elicits negative physical and emotional signs, called withdrawal syndrome. Different components of the withdrawal syndrome are thought to be mediated through distinct neural systems (Maldonado et al., 1992). In morphine-treated animals, infusion of opiate antagonists into the locus coeruleus (LC) (Aghajanian and Wang, 1987; Taylor et al., 1988) or the periaqueductal gray (Maldonado et al., 1992; Laschka et al., 1976) induced robust somatic withdrawal syndromes, whereas infusion into the NAc precipitated only a few somatic symptoms (Maldonado et al., 1992). Administration of opiate antagonists into the NAc and amygdala in morphine-dependent animals resulted in motivational withdrawal as well (Koob et al., 1989; Stinus et al., 1990). All things considered, these findings indicate the involvement of limbic structures in both somatic and motivational withdrawal. The involvement of the orexin system in the development of morphine dependence and emergence of withdrawal syndrome has been reported in several studies (Sharf et al., 2008; Azizi et al., 2010). Specifically, naloxone-induced precipitation of morphine withdrawal signs has been shown to be associated with increased c-Fos expression in LH orexin neurons (Georgescu et al., 2003), and in neurons of the NAc, VTA, and LC (Sharf et al., 2008). Orexin knock-out mice developed attenuated morphine dependence, as they displayed a less severe withdrawal syndrome (Georgescu et al., 2003). Systemic administration of an OX1R antagonist, SB-334867, attenuated precipitated morphine withdrawal syndrome in mice (Sharf et al., 2008). There is some evidence for the critical involvement of orexin-A and OX1Rs in the activation of brain stress system including the NAc shell, bed nucleus of stria terminalis, central amygdala, and hypothalamic paraventricular nucleus during morphine withdrawal (Laorden et al., 2012).

Blockade of dorsal hippocampal OX1Rs by SB-334867 prior to each morphine injection prevented the development of morphine dependence; however, a single injection of SB-334867 after the development of morphine-dependence did not prevent expression of the withdrawal syndrome (Hooshmandi et al., 2017). Orexin neurons heavily innervate the LC nucleus (Nambu et al., 1999) that is critically involved in drug withdrawal syndrome (Ivanov and Aston-Jones, 2001). Indeed, among various brain regions receiving orexinergic fibers, the LC receives the densest projections (Peyron et al., 1998). Opioid withdrawal syndrome is associated with an increase in the activity of LC neurons (Nunez et al., 2013). Local infusion of orexin-A into the LC elicited an OX1R-dependent withdrawal-like syndrome in chronically morphine-treated animals (Ghaemi-Jandabi et al., 2017). Conversely, blockade of LC OX1Rs prevented naloxone-elicited neuronal activation of LC neurons in morphine-dependent animals (Fakhari et al., 2017).

6. Modulation of the addictive properties of drugs of abuse by orexins

The orexin system is an important role player in addictive properties of opiates and exerts its effects through different brain areas. Animal studies have revealed that in the VTA orexin can provoke morphine preference in animals that had shown extinguished morphine-CPP, an effect that was blocked by systemic administration of SB-334867 (Aston-Jones et al., 2009). Direct involvement of the orexin neurons in the rewarding effect of morphine in the VTA has also been emphasized by other studies (Narita et al., 2006). In addition, orexin-A function in the insular cortex and LC reported to be involved in nicotine reinforcing effects (Hollander et al., 2008) and morphine somatic withdrawal syndromes (Azizi et al., 2010), respectively. In the NAc, while blockade of OX1Rs significantly decrease the expression of morphine-CPP, blockade of OX2Rs did not produce a similar effect (Sadeghzadeh et al., 2016). In the medial prefrontal cortex (mPFC) orexin enhanced mPFC-evoked responses in dopaminergic neurons once applied before mPFC stimulation. The application of orexin during the stimulation, however, resulted in an equal number of neurons showing enhanced and diminished evoked responses (Aston-Jones et al., 2009). Subsequent work showed that simultaneous release of the orexin into the VTA from LH when reward associated cues were presented could potentiate the responses of dopaminergic neurons of the VTA to the inputs from mPFC (Aston-Jones et al., 2010). In the CA1 region of the hippocampus, application of OX1R antagonist attenuated both the expression of morphine-CPP and maintenance of morphine rewarding properties (Farahimanesh et al., 2018). In the central nucleus of the amygdala (CeA), orexins increased firing rate of neurons (Bisetti et al., 2006). The CeA neurons innervate the orexin neurons in the LH (Nakamura et al., 2009). These studies emphasize the role of orexin signaling in different brain areas that are connected to the addiction-related behaviors.

7. OX1Rs represent a target for developing novel therapeutics for addiction

Previous reports strongly suggest that OXRs, particularly OX1Rs, represent a valuable target for the development of effective medication for the treatment of substance use disorders across a broad range of addictive drugs including marijuana (Flores et al., 2014), tobacco (Kenny et al., 2018; Hollander et al., 2008; LeSage et al., 2010), opioids (Sharf et al., 2010; Smith and Aston-Jones, 2012; Lupina et al., 2018), psychostimulants (Smith et al., 2009; Smith et al., 2010; Hutcheson et al., 2011), and alcohol (Anderson et al., 2014; Moorman and Aston-Jones, 2009). Although there are some indications of OX2Rs involvement in drug reward and craving (Farahimanesh et al., 2017; Zhang et al., 2007; Sadeghi et al., 2016; Ebrahimian et al., 2016), a wealth of evidence from preclinical studies suggests that a single orexin receptor antagonist (SORA) that specifically block OX1Rs (1-SORA) may hold more promising efficacy in the treatment of addiction. For instance, SB-334867 (a 1-SORA) decreased reinstatement of an extinguished cocaine-seeking elicited by drug-paired cues, but 4TP (a 2-SORA) failed to do so (Smith et al., 2009). SB-334867 also blocked footshock-induced reinstatement of cocaine-seeking behavior (Boutrel et al., 2005) and decreased cannabinoid intake and motivation to obtain the drug, but the 2-SORA TCS-OX2-29 failed to decrease cannabinoid intake (Flores et al., 2014).

On the other hand, studies on OX2Rs have also shown some positive results. For instance, while SB-334867 suppressed the acquisition and expression of morphine CPP in naïve, but not in morphine-dependent mice, TCS-OX2-29 suppressed CPP acquisition and expression in both naïve and morphine-dependent mice (Tabaeizadeh et al., 2013). Treatment with the 2-SORA JNJ-10397049 reduced ethanol self-administration, as well as the acquisition, expression, and reinstatement of ethanol CPP and ethanol-induced hyperactivity in mice. In contrast, the 1-SORA SB-408124 had no effect in reducing the reinforcing effects of ethanol (Shoblock et al., 2011). Systemically administered NBI-80713, a 2-SORA, decreased escalated heroin self-administration in rats with extended access to heroin, which is believed to model the transition from controlled drug use to compulsive-like drug-seeking and taking (Schmeichel et al., 2015).

Since orexin peptides have been implicated in the maintenance of arousal, several orexin receptor antagonists have been developed for the treatment of sleep disorders (Sakurai and Mieda, 2011). Although the pharmacology and kinetics of these antagonists are not optimal for treating substance use disorders, there are some promising signs (Khoo and Brown, 2014). For instance, almorexant, a dual orexin receptor antagonist (DORA), attenuated the expression of CPP to cocaine and amphetamine, though not to morphine (Steiner et al., 2013). Almorexant also reduced ethanol intake and its reinforcing efficacy

(breakpoint value in progressive ratio self-administration model) (Anderson et al., 2014). Suvorexant, an FDA-approved DORA to treat insomnia, attenuated cocaine self-administration and CPP, and reduced cocaine-induced elevations in ventral striatal dopamine (Gentile and Simmons, 2018). Suvorexant also modestly, albeit insignificantly, suppressed self-administration of the synthetic psychostimulant 3,4-methylenedioxypyrovalerone in rats (Simmons et al., 2017). On the other hand, TCS1102, a potent and selective DORA, which is used solely for preclinical research, failed to reduce nicotine self-administration, and cue-induced or nicotine-primed reinstatement of nicotine-seeking (Khoo et al., 2017).

8. Potential applicability of orexin antagonists in different phases of addiction

Addiction can be considered as a recurring cycle of three stages: binge-intoxication stage driven by the basal ganglia, withdrawal-negative affect stage driven by the extended amygdala, and preoccupation-anticipation (or craving) stage driven by the prefrontal cortex. This cycle worsens over time and involves neuroplastic changes in the brain reward, stress, and executive function systems (Koob and Volkow, 2016). Preclinical evidence indicates that SORAs and/or DORAs may bear beneficial effects in all of these stages. Since the orexin system is implicated in drug reinforcement and reward (Aston-Jones et al., 2010; Borgland et al., 2009), it is likely that SORAs and DORAs help addicts limit their drug use when they attempt to quit or when they relapse after a protracted period of abstinence. The notion is supported by a pile of preclinical evidence showing the effectiveness of SORAs and DORAs in reducing drug intake and motivation to take the drug (Table 2). In addition, orexin neurons appear to be an essential component of the brain circuitry responsible for the expression of withdrawal symptoms of drugs (see above). As a result, both local and systemic administration of SB-334867 (a 1-SORA) proved remarkably effective in attenuating morphine withdrawal syndrome (Sharf et al., 2008; Laorden et al., 2012; Hooshmandi et al., 2017; Mousavi et al., 2014). Therefore, a clinically administrable SORA would be theoretically beneficial for medically assisted detoxification. Finally, the orexin system contributes to the reinstatement of extinguished drug-seeking behavior (see above) (Harris et al., 2005; Boutrel et al., 2005). The 1-SORA SB-334867 consistently attenuated reinstatement of heroin, cocaine, and ethanol-seeking elicited after the extinction period (Table 2). As a result, clinically developed 1-SORAs may provide therapeutic benefit for preventing relapse in patients struggling to remain abstained from drugs. This multipotentiality of SORAs to be administered over the entire course of addiction and across a broad range of addictive drugs highlights their high applicability for the treatment of substance use disorders.

9. No candidate drug that targets OX1R has progressed into clinical development

Despite the wealth of animal studies supporting the role of OX1R signaling in drug reward and craving, clinical development of selective OX1R antagonists has not progressed adequately. This has been, in large part, due to the difficulties in finding drug candidates that specifically target OX1R without targeting OX2R. Among several OX1R antagonists that have been described thus far (Lebold et al., 2013; Roecker and Coleman, 2008; Coleman and Renger, 2010), SB-334867 was the most frequently used compound for targeting OX1R pathways *in vivo* and *in vitro* (Lebold et al., 2013). Despite its high selectivity (50 times greater for OX1R over OX2R) (Winrow and Renger, 2014), SB-334867 has poor pharmaceutical properties, in that it has low bioavailability (45.7% in rats) (Morairty et al., 2012) and stability (McElhinny et al., 2012). It may also cause unwanted side effects including abnormal posture and immobility when administered at high doses (30 mg/kg) (Nair et al., 2008). Additionally, relevant off-target affinities for the adenosine A2A and the 5-HT2C receptors have recently been reported (Lebold et al., 2013). Therefore, there is an unmet need for specific OX1R antagonists with desirable pharmaceutical properties that may serve as candidate therapies across various areas of drug addiction.

10. Potential side effects of orexin antagonists

The orexin system has been implicated in multiple physiological processes including motivation (Thompson and Borgland, 2011), arousal (Berridge et al., 2010; Boutrel and de Lecea, 2008), attention (Fadel and Burk, 2010), feeding and energy balance (Girault et al., 2012), and regulation of gastrointestinal functions (Okumura and Takakusaki, 2008). As a result, the clinical use of orexin antagonists is likely to be associated with some side effects including anhedonia, sleepiness, anorexia, weight loss, cataplexy, and functional gastrointestinal disorders (Khoo and Brown, 2014). Additionally, long-term suppression of the orexin system may precipitate in depressive-like symptoms (Yeoh et al., 2014). The clinical evidence is decreased orexin levels in the cerebrospinal fluid (CSF) of suicide patients with major depressive disorders (Brundin et al., 2007). Interestingly, CSF orexin levels increased at 6 and 12 months following the suicide attempt (Brundin et al., 2009). Similarly, preclinical studies indicated that early life stress and chronic stress were associated with a decrease in the activity of orexin neurons along with the behavioral symptoms of depressive-like phenotype (Lutter et al., 2008; James et al., 2014).

The profile and severity of the side effects may depend on the selectivity of the compound and its off-target activity. Randomized control trials that evaluated the efficacy and tolerability of suvorexant (a DORA) for the treatment of primary insomnia concluded that it was generally well tolerated (Tampi et al., 2018). However, some of the observed adverse events were somnolence, fatigue, dry mouth, dyspepsia, and peripheral edema (Tampi et al., 2018; Michelson et al., 2014). Suvorexant appeared to have abuse potential in healthy recreational polydrug users. This abuse liability was similar to zolpidem, but with a reduced incidence of abuse-related adverse events (Schoedel et al., 2016). A reverse-translational study demonstrated that chronic administration of suvorexant did not cause significant behavioral or withdrawal-related changes in rats, did not elicit complete cross-generalization to either zolpidem or morphine in rats, and did not show any behavioral evidence of positive reinforcing efficacy in monkeys (Born et al., 2017). Almorexant, a DORA that was advanced into clinical studies, increased sleep efficiency and total sleep time and reduced sleep latency and latency to REM sleep. No significant side effect or tolerability issues were noted (Hoever et al., 2012). However, an undisclosed tolerability issue resulted in the cessation of Phase III clinical development in 2011 (GlaxoSmithKline, 2011). Interestingly, a recent clinical trial that evaluated the efficacy and safety of almorexant in patients with chronic insomnia demonstrated that adverse events were similar with almorexant and placebo (Black et al., 2017).

11. Concerns on the translatability of preclinical evidence into human application

The most frequently used preclinical models in addiction research are intravenous self-administration and drug-induced CPP. These procedures model the positive reinforcing properties of addictive drugs (Heidbreder and Hagan, 2011). Typically, a fixed-ratio self-administration schedule replicates volitional drug-taking while a progressive-ratio schedule measures the motivation of a subject to obtain the drug (Spanagel, 2017). In addition, both paradigms can be reconstructed to model relapse to drug-seeking, which is indicative of craving (Spanagel, 2017). A critical issue about these procedures is how well they replicate the clinical aspects of addiction in drug users. Rationally, in order to extrapolate preclinical evidence to clinical application, there should be a robust face validity between the preclinical models and the DSM-5

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Table 2
Studies showing the effects of systemic administration of dual orexin receptor antagonists (DORAs) and single orexin receptor antagonists (SORAs) in animal models of drug abuse.

Selectivity	Compound	Model and drug	Main finding(s)	Reference
DORA	Almorexant (clinical development discontinued)	FR5 nicotine SA in rats	Decreased nicotine intake; Decreased food pellet SA	(LeSage et al., 2010)
		Morphine, amphetamine, or cocaine CPP in rats	Decreased expression of cocaine and amphetamine CPP; Had no effect on the expression of morphine CPP; Decreased expression of morphine-induced locomotor sensitization	(Steiner et al., 2013)
		2-bottle choice ethanol consumption; PR ethanol SA in rats Drinking in the dark in mice	Decreased ethanol and water intake; Decreased motivation to consume ethanol; Decreased binge-like ethanol drinking	(Anderson et al., 2014)
DORA	Suvorexant (FDA-approved for insomnia)	PR cocaine SA; cocaine CPP in rats	Decreased motivation to obtain cocaine; Slightly attenuated acquisition of cocaine CPP; Had no effect on cocaine-induced hyperlocomotion	(Gentile and Simmons, 2018)
		FR1 MDPV SA in rats	Had no significant effect on MDPV intake; Increased time to retrieve initial ten MDPV infusions	(Simmons et al., 2017)
1-SORA	SB-334867	FR5 nicotine SA; PR nicotine SA; ICSS thresholds in rats	Decreased nicotine intake; Decreased motivation to obtain nicotine; Abolished the stimulatory effects of nicotine on brain reward circuitries; Had no effect on food pellet self-administration	(Hollander et al., 2008)
		FR5 nicotine SA in rats	Decreased nicotine intake; Had no effect on food pellet SA	(LeSage et al., 2010)
		FR1 heroin SA; PR heroin SA in rats	Decreased heroin intake; Decreased motivation to obtain heroin; Decreased cue-induced reinstatement of heroin seeking; Had no effect on heroin-induced reinstatement of heroin seeking	(Smith and Aston-Jones et al., 2012)
		Morphine-induced sensitization in mice; Morphine and cocaine CPP in mice	Decreased morphine CPP; Had no effect on cocaine CPP; Had no effect on acute locomotor and sensitization responses to morphine	(Sharf et al., 2010)
		Morphine-induced sensitization in mice	Inhibited the acquisition of morphine-induced sensitization to locomotor activity	(Lupina et al., 2018)
		Morphine CPP in mice	Decreased acquisition and expression of morphine CPP in naïve mice, but not in morphine-dependent mice	(Tabaeizadeh et al., 2013)
1-SORA	SB-334867	FR1 cocaine SA in rats	Decreased cocaine-seeking following 1 day or 2 weeks of abstinence; Decreased context-induced reinstatement of cocaine-seeking	(Lupina et al., 2018)
		FR cocaine SA; amphetamine CPP in rats	Decreased acquisition and expression of cocaine-seeking; Decreased expression of amphetamine CPP	(Hutcheson et al., 2011)
		FR1 cocaine SA in rats	Had no effect on an established cocaine intake; Had no effect on late extinction session responding; Had no effect on learning cocaine-stimulus associations; Decreased cue-induced reinstatement of cocaine-seeking	(Smith and Aston-Jones et al., 2012)
		FR1 cocaine SA in rats	Decreased footshock-induced reinstatement of cocaine-seeking	(Boutrel et al., 2005)
		FR1 cocaine SA in rats	Decreased cue-induced reinstatement of cocaine-seeking; Had no effect on cue-induced reinstatement of sweetened condensed milk SA	(Martin-Fardon and Weiss, 2014a,b)
		PR cocaine SA in rats	Decreased consumption and appetitive responding for low dose cocaine; Decreased appetitive, but not consumption, responding for high dose cocaine; Had no effect on sleep/wake patterns	(Brodnik et al., 2015)
1-SORA	SB-334867	FR1 and PR cocaine SA in short and long access rats	Decreased escalated cocaine intake in long access, but not in short access rats; Decreased motivation to obtain cocaine in short and long access rats	(Schmeichel et al., 2017)
		WIN55212-2 SA in mice	Decreased acquisition of cannabinoid SA; Decreased cannabinoid intake; Decreased motivation to obtain cannabinoid; Had no effect on water-maintained operant behavior	(Flores et al., 2014)
		2-bottle choice ethanol consumption; PR ethanol SA in rats Drinking-in-the-dark in mice	Decreased ethanol intake; Had no effect on motivation to consume ethanol; Decreased binge-like ethanol drinking	(Anderson et al., 2014)
		FR3 ethanol SA in rats	Decreased ethanol intake; Decreased cue-induced reinstatement of alcohol-seeking; Had no effect on responding for water	(Lawrence et al., 2006)
		FR3 and PR ethanol SA in rats	Decreased ethanol intake; Decreased sucrose intake; Decreased motivation to consume ethanol; Had no effect on motivation to consume sucrose	(Jupp et al., 2011)
		Ethanol SA in rats	Decreased cue-induced reinstatement of ethanol-seeking; Had no effect on the reinstatement of glucose/saccharine seeking	(Martin-Fardon and Weiss, 2014a,b)
1-SORA	SB-408124	FR3 ethanol SA in rats; Ethanol withdrawal in rats; ethanol CPP in mice	Had no effect on ethanol intake, saccharine intake, the acquisition and expression of ethanol CPP, ethanol-induced hyperactivity, and signs of ethanol withdrawal	(Shoblock et al., 2011)

(*continued on next page*)

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Table 2 (*continued*)

Selectivity	Compound	Model and drug	Main finding(s)	Reference
2-SORA	NBI-80713	Short and long access heroin SA in rats	Decreased heroin SA in long access, but not in short access rats; Had no effect on food pellet SA	(Schmeichel et al., 2015)
	TCS-OX2-29	Morphine CPP in mice	Decreased acquisition and expression of morphine CPP in naïve and morphine-dependent mice	(Tabaeizadeh et al., 2013)
		WIN55212-2 SA in mice	Had no effect on the acquisition of cannabinoid SA, cannabinoid intake, motivation to obtain cannabinoid, and water-maintained operant behavior	(Flores et al., 2014)
	4PT	FR1 cocaine SA in rats	Had no effect on established cocaine intake, late extinction session responding, learning cocaine-stimulus associations, and cue-induced reinstatement of cocaine-seeking	(Smith et al., 2009)
	LSN2424100	2-bottle choice ethanol consumption; PR ethanol SA in rats Drinking-in-the-dark in mice	Had no effect on ethanol intake; Decreased motivation to consume ethanol; Decreased binge-like ethanol drinking	(Anderson et al., 2014)
2-SORA	JNJ-10397049	FR3 ethanol SA in rats; Ethanol withdrawal in rats; Ethanol CPP in mice	Decreased ethanol intake; Had no effect on saccharine intake; Blocked acquisition, expression, and priming-induced reinstatement of ethanol CPP; Blocked ethanol-induced hyperactivity; Had no effect on signs of ethanol withdrawal	(Shoblock et al., 2011)

1-SORA, single orexin receptor type 1 antagonist; 2-SORA, single orexin receptor type 1 antagonist; 4PT, 4-pyridylmethyl (S)-tert-leucyl 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline; CPP, conditioned place preference; DORA, dual orexin receptor antagonist; FR1, fixed-ratio 1 schedule; ICSS, intracranial self-stimulation; MDPV, 3,4-methylenedioxypyrovalerone; OX1R, orexin receptor 1; OX2R, orexin receptor 2; PR, progressive ratio schedule; SA, self-administration.

criteria of substance use disorders. The face validity refers to the degree to which the models are effective in measuring what they aim. As a result, drug-reinforced behavior cannot be considered as an animal counterpart of human addiction (Piazza and Deroche-Gamonet, 2013). As previously stated, the three stages of transition to addiction include recreational, escalated, and compulsive drug use. Self-administration paradigms using unit drug doses above the median effective dose (ED50), fixed-ratio schedules, and short access to the drug for short periods of time (1–3 h for 2–4 weeks) are considered as the models of recreational drug use (Piazza and Deroche-Gamonet, 2013). Self-administration methods using low unit doses of drugs (Piazza et al., 1989) or alternatively with long daily access to the drug (6–12 h) (Ahmed and Koob, 1998) are models of escalated drug use as they bring about rapid escalation of drug intake in high-responder rats. Finally, prolonged self-administration of a drug (3 months) appears to cause addiction-like behaviors, in that it provokes behaviors that resemble three of the essential diagnostic criteria for addiction: difficulty in stopping drug use, having extremely high motivation to take the drug, and continued drug use despite adverse consequences (Deroche-Gamonet et al., 2004). In sum, current preclinical evidence that supports potential therapeutic uses for DORAs and SORAs in the treatment of addiction is still preliminary and should be interpreted with the highest caution.

12. Concluding remarks

Researchers and pharmaceutical companies have developed an interest in the orexin system over the past 20 years. Although the orexins were first noted for their roles in energy homeostasis, many studies since 1998 have highlighted their key roles in addiction. The extent to which OX1Rs and OX2Rs are involved in each of the physiological functions is still an area of controversy, but we have currently enough evidence at hand to know that the development of new agents targeting these receptors, either in form of single orexin receptor antagonists or as dual orexin receptor antagonists, can be beneficial for the treatment of addiction to certain drugs of abuse. Our current knowledge indicates that OX1Rs represent a target for developing novel therapeutics for addiction, but considering the complicated interactions among stress, anxiety, and compulsive and addictive behaviors one shall still consider possible positive effects resulted from OX2Rs manipulations. Future animal research as well as clinical studies with novel SORA and DORA compounds will guide us in our future efforts for developing effective medication.

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Appendix A. Supplementary data

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