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Introduction to the Special Issue: “Making orexin-based therapies for addiction a reality: What are the steps from here?”

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More than fifteen years of animal studies indicate that the brain's orexin (hypocretin) system is a promising target for developing medications to treat addiction (James et al., 2017b).

Orexin neurons are more numerous in animals and human subjects with a history of drug abuse (James et al., 2018b; Pantazis et al., 2019; Thannickal et al., 2018), and pharmacological compounds that block signaling at the orexin 1 receptor (Ox1R) are highly effective at reducing drug craving and seeking for all drugs of abuse tested, including cocaine, opioids, nicotine and alcohol (Bentzley and Aston-Jones, 2015; Fragale et al., 2019; Harris et al., 2005; James et al., 2018a; Lawrence et al., 2006; Mohammadkhani et al., 2019a; Moorman et al., 2017; Plaza-Zabala et al., 2013). In light of these data, the National Institute on Drug Abuse (NIDA) Division of Therapeutics and Medical Consequences recently identified orexin receptor modulators as a mechanism of ‘highest priority’ for the development of new medications for addiction (Rasmussen et al., 2019). This undertaking is particularly urgent given the opioid crisis that is currently devastating the United States. To this end, this *Special Issue* of *Brain Research* brings together experts from the drug-discovery, clinical and preclinical fields with the view to provide an update regarding orexin modulators as therapeutics for addiction and related psychiatric disorders. In addition, we seek to identify key outstanding questions and concerns that must be addressed to optimize the efficacy of these compounds and to expedite their transition to clinical trials.

Our special issue begins with two brief reviews of orexin neuron connectivity and function. Liu et al. (2018) summarize recent efforts to characterize orexin neurocircuitry, with a focus on synaptic inputs onto orexin neurons and their downstream brain targets. Burdakov (2018) focuses on two distinct orexin output circuits that govern context-appropriate action selection. We then narrow our focus to orexin's role in addiction, with three review articles

that together provide an up-to-date overview of preclinical studies investigating orexin system function in abuse of psychostimulants, opioids and alcohol. Simmons & Gentile (2019) summarize current knowledge on how orexin mediates cocaine reward via interactions with mesoaccumbens, tegmental, habenular, pallidal and preoptic circuits. Zarrabian et al. (2018) provide an overview of data linking the orexin system to opioid reward, including evidence that orexin signaling is involved in the expression of the morphine withdrawal syndrome. Finally, Campbell et al. (2018) summarize preclinical data testing the efficacy of single and dual orexin receptor antagonists (SORAs and DORAs, respectively) on behavioral processes associated with alcohol use disorder, including relapse to alcohol seeking, alcohol withdrawal symptoms and sleep. A common theme to arise from these articles is the importance of Ox1R signaling in mediating drug-seeking behaviors, pointing to the potential utility of selective Ox1R antagonists (1-SORAs) for the treatment of addiction. However, a handful of studies indicate that some aspects of opioid and alcohol addiction are also dependent on Ox2R signaling (Brown et al., 2013; Schmeichel et al., 2015), thus raising the possibility that dual orexin receptor antagonists may have some advantage for treating these addictions.

Given the immense interest in 1-SORAs as potential therapeutics for addiction and other motivational disorders, significant effort has been recently dedicated to the development of these compounds. In their review article, Perrey & Zhang (2018) provide a comprehensive and up-to-date overview of the Ox1R antagonists reported thus far, with an emphasis on newly disclosed compounds. The authors note that to date, 1-SORAs have been largely 'byproducts' of dual antagonist development for the treatment of sleep disorders, but speculate that more resources will be dedicated to the development of 1-SORAs in light of the opioid epidemic and increasing evidence implicating Ox1R signaling in addiction.

Currently, the dual orexin receptor antagonist suvorexant (Belsomra™) is the only clinically available orexin receptor antagonist. Given its strong safety and tolerability profile (Owen, 2016), significant recent discussion has focused on the potential repurposing of this drug for the treatment of addiction (James et al., 2017b). To this end, Suchting and colleagues (2019) describe results from the first examination of suvorexant's effects on addiction-related indices in non-treatment seeking subjects with cocaine use disorder. Patients received daily treatment with suvorexant or placebo on an escalating dose schedule for 2 weeks (10 mg week 1, 20 mg week 2). Suvorexant treatment was associated with improved sleep, reduced physiological measures in response to acute stress, and reduced cocaine craving. Urine toxicology indicated no change in cocaine use per se, although the authors note that changes in cocaine use patterns may not have been expected as participants were non-treatment seeking and did not endorse a readiness or willingness to change, which is often required to achieve initial abstinence (Wardle et al., 2016). Regardless, suvorexant-associated reductions in the cognitive-behavioral and physiological processes reported here provide promising initial evidence to support future studies designed to study suvorexant's efficacy in reducing primary addiction outcomes in treatment-seeking populations.

To date, the majority of preclinical studies have focused on testing the acute effects of 1-SORAs and DORAs on addiction-related behaviors. Here, two separate research groups provide new data showing that the effects of orexin receptor antagonists persist beyond the

pharmacological availability of these compounds. Mohammadkhani et al. (2019b) report that when administered systemically, 1-SORA SB334867 (SB; 30 mg/kg) reduced economic demand for the opioid remifentanyl for up to 24 h post-administration. Brodnik et al. (2018) report that the same dose of SB reduces cocaine self-administration up to 21 h later. Given the relatively short half-life of the SB compound (~0.4 h), these data imply that SB treatment induces persistent neuroadaptations that persist beyond the bioavailability of the drug to negatively regulate drug-seeking behavior. Indeed, using a different selective Ox1R antagonist (RTIOX-276), Brodnik et al. show that systemic treatment is associated with decreased dopamine transporter phosphorylation in nucleus accumbens at 24 h post-treatment, which corresponded with reduced dopamine uptake inhibition by cocaine. These findings raise important questions relating to the potential dosing regimen of orexin receptor antagonists for addiction; it is possible that daily dosing may not be necessary to suppress craving across multiple days, however this needs to be tested directly. Also notable, Mohammadkhani report that persistent effects of SB are even more pronounced when delivered intraperitoneally (ventral pallidum); in this case, effects were observed for up to 72 h which has important implications for experimental designs of similar studies going forward.

In addition to regulating motivation for drugs of abuse, there is a known role for the orexin system in mediating appetite and feeding behavior (Mahler et al., 2014). In her article, Barson (2018) proposes a fundamental role for the orexin system in promoting foraging for food under conditions of limited availability. She does this in the context of an overview of evidence linking the orexin system to homeostatic food intake as well as dysregulated eating such as excessive or binge-like food intake. Of particular note in the context of this *Special Issue*, evidence indicates that binge-like feeding is blocked by orexin receptor antagonists at doses lower than those required to suppress homeostatic feeding. These data parallel those from the addiction field showing greater effects of low-dose SB in rats that exhibit higher addiction like behaviors (Fragale et al., 2019; James et al., 2018a; Moorman et al., 2017), and together indicate that low doses of orexin receptor antagonists may be effective at reducing craving for drugs of abuse or highly salient food (e.g. high fat, high sugar), without affecting normal eating and weight maintenance. Teegala et al. (2018) extend evidence implicating orexin in homeostatic feeding by showing that signaling at Ox1R mediates increased NMDA current amplitude in ventral tegmental area under low glucose conditions. The authors also show that increasing glucose concentration in lateral hypothalamus is sufficient to reduce conditioned place preference for palatable food in weight-restricted rats, indicating that the glucose sensing mechanism of orexin neurons (the majority of which are inhibited by glucose) could be a therapeutic target for aberrant food seeking behaviors. It is unclear if a similar mechanism could be targeted to reduce other reward behaviors, such as drug seeking.

Notably, the orexin system has been implicated in several stress-related psychiatric states, many of which are often comorbid with substance use disorders, including anxiety, depression, panic and fear. This raises the possibility that orexin receptor antagonists may have additional utility in treating these disease states whether they manifest in isolation or in conjunction with addiction (James and Aston-Jones, 2017; James et al., 2017a; Yeoh et al., 2014). Shekhar and colleagues (Abreu et al., 2018) present a comprehensive overview of

evidence implicating medial (DMH/PF) orexin populations in the regulation of hypertension and the expression of panic and phobic responses. The authors note that these processes appear to be largely mediated by Ox1R signaling, thus supporting the development of 1-SORA antagonists for treating panic and stress-induced symptoms. In a closely related article, Soya & Sakurai (2018) describe a circuit through which orexin acts at Ox1Rs on locus coeruleus norepinephrine neurons to mediate expression of fear-related behavior, indicating that 1-SORAs may also be useful for treating excessive fear or overgeneralization in anxiety or post-traumatic stress disorder (PTSD). In their article, Summers et al. (2018) contrast the anxiogenic properties of Ox1R signaling with new evidence indicating that signaling at Ox2Rs promotes stress resilience, as well as anxiolytic and antidepressive behavior. These data are discussed in the context of potential clinical implications of DORAs for stress-related (and other) disorders; particularly salient here is evidence from a clinical trial indicating that suvorexant treatment was associated with a worsening in the severity of depression symptoms in renal dialysis patients with comorbid insomnia and major depressive or generalized anxiety disorders (Petrus and Furmaga, 2017). Grafe and Bhatnagar (2018) provide an important overview of sex differences in orexin function and how these may contribute to differential stress behaviors. Of note, preclinical data generally point to higher orexin system activity in females, which contributes to exaggerated neuroendocrine and behavioral responses to stress. The authors thus argue that these findings might point to the need for sex-specific guidelines in dosing for any future orexin-based therapeutic. Together, these data indicate that 1-SORAs may have anxiolytic properties useful for the treatment of several stress-related disorders; in the case of addiction, such compounds might reduce drug craving while simultaneously ameliorating anxiety symptoms, which are highly comorbid with substance abuse and can emerge de novo during withdrawal (Gawin, 1991; Grant et al., 2004). Further studies are required to understand the implications of compounds that act at Ox2Rs, including suvorexant, on anxiety and depressive symptomology, and appropriate dosing regimens for males vs. females.

Orexin neurons also convey cognitive and attentional functions, largely via their dense projections to several key arousal systems, including locus coeruleus and basal forebrain cholinergic neurons (Baldo et al., 2003; Espana et al., 2005). This theme is explored here by three experimental papers that each present new data relating to the orexin system and arousal/cognition. Freeman & Aston-Jones (2018) compare Fos expression in medial (DMH/PF) vs. lateral (LH) orexin neurons during a Go/No-Go task in rats. Activation of medial, but not lateral, orexin neurons was positively correlated with greater accuracy on the Go/No-Go task, providing correlative evidence for this subpopulation of neurons in response inhibition. Calva and Fadel (2018) present new data indicating that intranasal delivery of a modified orexin B peptide in rat is associated with enhanced neural activity in several distinct cortical and basal forebrain areas. Together with previous evidence that intranasal delivery of Orx A results in widespread activation of arousal regions (Calva et al., 2018) and improves cognition in narcoleptic and sleep deprived patients (Weinhold et al., 2014), these data point to the potential clinical utility of intranasal orexin administration in treating cognitive dysfunction. Wiskerke et al. (2019) present evidence that systemic pretreatment with the 1-SORA antagonist SB has minimal effects on response inhibition or attentional functioning (ability to wait) on a rat version of the stop signal test. Together, these studies

point to a complex role for the orexin system in cognition, and highlight the need for further studies to test for the potential implications of therapeutics that block orexin signaling across a range of cognitive/attentional assays.

Thus, this special issue raises several key takeaway points that will be critical for guiding the development and optimization of orexin-based therapeutics for the treatment of addiction. First, the majority of preclinical data indicate that priority should be given to developing and testing 1-SORAs for addiction therapeutics, given the overwhelming evidence implicating Ox1R signaling in motivation for salient rewards. However, it is clear that the role of Ox2R in addiction is understudied and thus warrants significant attention going forward, especially given evidence that Ox2R antagonists attenuate addiction behaviors under some circumstances. Second, in light of the promising preliminary clinical trial data reported here by Suchting et al. (2019), it is critical that the potential repurposing of suvorexant for the treatment of addiction be explored with urgency. Several questions remain regarding efficacy of suvorexant in reducing craving for other drugs of abuse (including opioids), as well as the potential safety implications of coadministration of suvorexant with other medications (e.g. buprenorphine), however the fact that this compound is already clinically available for another indication (insomnia) makes it a highly attractive option for the timely clinical uptake of orexin-based therapies for addiction (James et al., 2020). Third, orexin system modulators will likely have therapeutic benefits for other stress-related psychiatric symptoms that are often comorbid with addiction, including anxiety and panic, thus potentially maximizing their efficacy in these patients. Finally, it is incumbent on researchers to address key outstanding questions relating to the potential clinical use of orexin modulators for addiction. For example, how might SORAs/DORAs be used in combination with other existing treatments (e.g. psychotherapy) and medications for addiction? What are the consequences of long-term (chronic) dosing with orexin receptor antagonists? Are SORAs/DORAs effective in reducing craving in polydrug abusing patient populations? Do differences in orexin system function between sexes mandate different prescription guidelines for males vs. females? In sum, there is reason for significant optimism with respect to the potential utility of orexin modulators for the treatment of addiction. We hope that the conclusions drawn from this *Special Issue* will act as a roadmap for interdisciplinary studies involving drug discovery, basic/preclinical studies and clinical trials, that are designed to optimize and accelerate the clinical use of these compounds.

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