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The hypocretin/orexin system as a target for excessive motivation in alcohol use disorders

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Abstract

The hypocretin/orexin (ORX) system has been repeatedly demonstrated to regulate motivation for drugs of abuse, including alcohol. In particular, ORX seems to be critically involved in highly motivated behaviors, as is observed in high-seeking individuals in a population, in the seeking of highly palatable substances, and in models of dependence. It seems logical that this system could be considered as a potential target for treatment for addiction, particularly alcohol addiction, as ORX pharmacological manipulations significantly reduce drinking. However, the ORX system also plays a role in a wide range of other behaviors, emotions, and physiological functions and is disrupted in a number of non-dependence-associated disorders. It is therefore important to consider how the ORX system might be optimally targeted for potential treatment for alcohol use disorders either in combination with or separate from its role in other functions or diseases. This review will focus on the role of ORX in alcohol-associated behaviors and whether and how this system could be targeted to treat alcohol use disorders while avoiding impacts on other ORX-relevant functions. A brief overview of the ORX system will be followed by a discussion of some of the factors that makes it particularly intriguing as a target for alcohol addiction treatment, a consideration of some potential challenges associated with targeting this system and, finally, some future directions to optimize new treatments.

Keywords

hypothalamus; neuropeptide; ethanol; dependence; alcoholism; craving

1. Introduction

Drug and alcohol use disorders form a cluster of serious mental diseases that have enormous impact both in the United States and around the world. The legality and accessibility of alcohol make it, along with tobacco, the most widely abused drug in the United States (Center for Behavioral Health Statistics and Quality 2016). Consequently, the prevalence of alcohol use disorder (AUD) is particularly high: over 15 million adults in the United States exhibit AUDs (Center for Behavioral Health Statistics and Quality 2016), and approximately 76.3 million people have been diagnosed with an alcohol use disorder globally (World

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Health Organization 2014). Alcohol misuse is estimated to be the leading cause of death among people between the ages of 15–49 (Lim et al. 2012). As such, it is imperative that new preventions and treatments for AUDs, along with other addictions and mental disorders, are actively pursued. Despite some promising leads such as naltrexone, topiramate, acamprosate, baclofen, and other pharmacotherapies, there have been no silver bullets for treating AUDs (Palpacuer et al. 2017). Given the sophistication of research underlying the development of these potential treatments (Litten et al. 2016), their lack of complete efficacy suggests that alternate strategies or targets for treatment are worth exploring.

Important questions that arise when considering potential treatments for AUDs and other addictions include, "what are the preferred outcomes?" and "what side effects or lack of selectivity are acceptable in treatment application?" Historically, the optimal outcome for treatment of AUDs has been abstinence, and research has focused on removing the motivation to consume alcohol (Warren and Hewitt 2010). From a harm-reduction perspective this is a logical and valuable goal. If a patient has problems with the use of alcohol and it is possible to completely suppress alcohol seeking and consumption in this patient, then the clinical problems stemming from over-use of alcohol are solved. For a number of reasons, however, achieving this goal in a reliable fashion has been challenging. This may stem from the fact that motivation for alcohol is a complex, nuanced suite of behaviors driven by a multitude of neural circuits and modulatory systems, and that we have not yet identified the precise network, or combination of networks, necessary to selectively suppress alcohol use (Koob 2014; Koob and Volkow 2016). It may also be the case that removing the drive to consume alcohol, while preserving all other natural motivated behaviors (appetitive, social, etc.), is too complex – these drives may be inextricably linked. The consequence of treatments that drag down natural motivation along with motivation for alcohol is that quality of life is often impaired during treatment maintenance, and medication adherence becomes difficult, ultimately resulting in relapse and prolongation of the disease. An alternate possible strategy for treating AUDs is to target the aspect of addiction that embodies the clinical aspect of the disorder – the hyperactive drive for alcohol. So rather than attempting to quash alcohol motivation completely, a potentially promising avenue might be to target neural systems specifically associated with the intermediate stages between regulated and problematic alcohol use. Put simply, treatments that transform or return alcoholic patients into individuals with the capacity for controlled drinking, and who have normal alternate motivational drives, might have a higher likelihood of prolonged maintenance. This strategy could improve the quality of life in patients relative to living with AUDs or living with non-selective treatments. Such treatments could also provide options – abstinence might be optimal for some, whereas regulated, non-problematic alcohol use might work for others. It should be noted that the immediate need for treating patients with AUDs is to save their lives and the quality of their lives and those around them (including society as a whole). In this context, all treatments that produce a reduction in problematic drinking, including those currently successfully employed, are valuable and should be continued until more advanced options are developed. However, considering a future goal of treatment with greater specificity for addiction itself, while preserving natural levels of motivation (even potentially for alcohol), could be a valuable enterprise in the meantime.

One neural system that may be an important target for developing this addiction-specific treatment strategy is the hypocretin/orexin (ORX) hypothalamic neuropeptide system. This system has been repeatedly demonstrated to play roles in highly motivated behaviors as well as in some of the negative components of behavior, such as stress, that further drive problematic alcohol use. This review will discuss aspects of the ORX system that support its evaluation as a possible target with a specific focus on the heightened motivation associated with addiction, particularly alcohol addiction, while sparing other aspects of natural motivated behavior. There are challenges associated with developing the ORX system as a target for AUDs, including the fact that it plays a role in a wide and diverse range of behaviors and physiological functions. It is also the case that identifying a single target for addiction treatment may be an overly simplistic strategy – chronic administration of ethanol likely results in a number of simultaneous neuroadaptations and may additionally stem from a complex set of genetic or epigenetic elements that prime the system for potential abuse. Thus, although the focus of this review is on a particular signaling system, the ORX system may function as a component of a multifaceted treatment strategy. This and other future goals for identifying neural substrates of AUDs will be considered with the hope that a better understanding of how this system works, both within and outside of the context of alcohol use, may provide insight into how AUDs and other addictions might treated.

There have been a number of reviews on the role of the ORX system in drug abuse and addiction (Aston-Jones et al. 2009; Aston-Jones et al. 2010; Baimel and Borgland 2017; Boutrel and de Lecea 2008; James et al. 2017b; Plaza-Zabala et al. 2012), including some excellent reviews addressing the role of ORX in alcohol use and AUDs (Barson and Leibowitz 2016; Brown and Lawrence 2013; Lawrence 2010; Mahler et al. 2012b; Walker and Lawrence 2017), as well as focusing on the role of the ORX system in heightened motivational states (Mahler et al. 2014). The goal of this review, therefore, is to attempt to align the specific aspects of ORX signaling that underlie its role in intense motivation with the prominent role of the system in regulating alcohol use. Together, these aspects of ORX signaling make the case that this system, whether independently or in conjunction with other neural networks, may be a key element of this advanced, addiction-targeted treatment of AUDs.

2. Brief overview of the hypocretin/orexin system

Hypocretins/orexins (ORX) are peptides synthesized exclusively by neurons located in the lateral hypothalamic area – a region made up of the lateral, perifornical, and dorsomedial hypothalamus – and in regions of the subthalamus including the zona incerta and subthalamic nuclei (Sakurai et al. 1998). This system was separately discovered by two groups in 1998, naming it orexin (Sakurai et al. 1998) and hypocretin (de Lecea et al. 1998). ORX neurons synthesize the prepro peptide preproorexin (preprohypocretin), which is cleaved into two peptides: orexin-A/hypocretin-1 and orexin-B/hypocretin-2. Despite the small number of neurons expressing ORX – approximately 3,000 in rats and 70,000 in humans (Nambu et al. 1999; Peyron et al. 1998) – these neurons have a profound influence over a wide range of behaviors, in part due to their widespread projections across the extent of the neuraxis (Date et al. 1999; Nambu et al. 1999; Nixon and Smale 2007; Peyron et al. 1998; van den Pol 1999).

ORX-A/B binds to one of two receptors: OX1R/HCRT1R and OX2R/HCRT2R. The OX1R is more selective for ORX-A over ORX-B whereas the OX2R binds both peptides approximately equally (Sakurai 2014). Although ORX-A and ORX-B are approximately equally co-localized in neurons and projections, there is a differential distribution of OX1R vs. OX2R across different brain regions (Trivedi et al., 1998; Hervieu et al., 2001; Marcus et al., 2001; Cluderay et al., 2002). Some have proposed that this differential distribution indicates separable roles for the these signaling pathways with OX1R being more associated with areas involved in motivation such as medial prefrontal cortex (mPFC) and amygdala and OX2R more densely located in brain regions more associated with regulation of sleep and arousal such as hypothalamic and brainstem nuclei (Sakurai 2014). Although pharmacological manipulation of these receptors does suggest that there are differential functions roughly corresponding to these general categories, they are far from exclusive, and likely not due to categorical functions of the locations of OX1R vs. OX2R. For example, OX1R is the main receptor subtype in the locus coeruleus, and OX2R is the main receptor subtype in the nucleus accumbens (NAc) shell (Cluderay et al. 2002; Hervieu et al. 2001; Marcus et al. 2001; Trivedi et al. 1998). Combined with the fact that many of the brain areas expressing ORX receptors are involved in multiple behaviors and functions, a circuit, as opposed to structural, explanation for differences in function, may be warranted. Along these lines, in addition to differential receptor distribution, ORX heterogeneity may result from different subpopulations of neurons within the lateral hypothalamic area. As summarized in a number of reviews (Harris and Aston-Jones 2006; James et al. 2017b), neurons in the lateral hypothalamic subregion appear to more consistently play a role in reward motivation whereas neurons in the perifornical and dorsomedial regions are more activated by stress and arousal.

ORX neurons also express and signal with a number of other neurotransmitters and neuromodulators. These include glutamate which, in combination with ORX, has an overall excitatory impact on target neurons (Rosin et al. 2003; Schone et al. 2014), as well as dynorphin, which has a predominantly inhibitory effect (Li and van den Pol 2006). Exactly what function this multiplexing of chemical signaling plays in conveying information is currently poorly understood. However, a number of recent studies have begun investigating the combined impact of ORX and dynorphin on major target structures such as the ventral tegmental area (VTA) and the paraventricular nucleus of the thalamus (PVT) (Baimel et al. 2017; Matzeu et al. 2017; Muschamp et al. 2014). Additional work has begun on understanding the fast excitatory signaling of glutamate vs. the relatively slower peptidergic excitatory signaling of ORX in this population of neurons (Schone et al. 2014; Schone and Burdakov 2017; Schone et al. 2012). Although much research investigating the role of the ORX system in motivation and addiction has focused on pharmacological dissection of receptor stimulation, the modern appreciation that ORX neurons (among others) signal using multiple neurochemicals, perhaps simultaneously, indicates that we have more to learn about how such complex systems regulate behavior, including those directed towards alcohol and other drugs of abuse.

3. The hypocretin/orexin system and non-alcohol drugs of abuse

Initial reports of the ORX system characterized two main functions: a role in feeding, demonstrated by increased food consumption following ICV ORX administration (Sakurai et al. 1998), and a role in regulating sleep and arousal, as demonstrated initially by the close association between ORX neuron, peptide, and receptor loss and narcolepsy with cataplexy (Lin et al. 1999; Nishino et al. 2000; Thannickal et al. 2000). Since these early observations there has been a striking number of behaviors and functions closely tied to activation of the ORX system. Two of the more prominent associations are with overall motivation for reward (including drugs of abuse such as alcohol), and stress and anxiety (Aston-Jones et al. 2009; Aston-Jones et al. 2010; Berridge et al. 2010; Cason et al. 2010; Giardino and de Lecea 2014; James et al. 2017a; James et al. 2017b; Kuwaki and Zhang 2012; Mahler et al. 2014; Tsujino and Sakurai 2013). These two drives are of particular interest in the context of drug and alcohol abuse, as both reward motivation and increasing levels of stress are major contributors towards problematic substance use (Koob 2009; Koob et al. 2014; Wise 2013; Wise and Koob 2014). The following sections address the ORX system in the context of motivation for non-alcohol drugs of abuse (Section 3) and for alcohol (Section 4). An additional discussion of non-motivation functions of the ORX system, including stress, in Section 5 informs the question of how motivation-specific ORX activity may be targeted for AUDs or other addiction-associated behavior.

The role of the ORX system in drug motivation has been the subject of numerous reviews (Baimel et al. 2015; Baimel and Borgland 2017; James et al. 2017b; Mahler et al. 2012b). As such only a short description follows and the reader is recommended to some of these more comprehensive discussions. Although the broad category of drugs of abuse necessarily includes alcohol, early studies of the role of the ORX system in addiction-associated behaviors focused on other drugs such as opiates, psychostimulants, and nicotine, and a considerable amount of research has connected ORX function with motivation for these substances. Thus before focusing specifically on the alcohol in Section 4, a brief consideration of ORX and non-alcohol drugs of abuse is useful for contextualization.

Early studies demonstrated that ORX neurons are activated by withdrawal from and seeking of multiple drugs of abuse (Georgescu et al. 2003; Harris et al. 2005), that stimulation of ORX neurons increases drug seeking (Harris et al. 2005), and that antagonism of ORX signaling, particularly through the OX1R, decreases reinstatement of cocaine seeking (Boutrel et al. 2005; Harris et al. 2005). Since these early studies, many groups have demonstrated similar findings, consistently showing that the ORX system is activated by, and that suppression of ORX signaling has a negative impact on, drug seeking. Of note, the influence of ORX appears to span multiple drug classes, having control over the preference for and seeking of cocaine and amphetamines, opiates, and nicotine, among others (Baimel et al. 2015; Hollander et al. 2008; Mahler et al. 2012b; Plaza-Zabala et al. 2013a; Smith and Aston-Jones 2012), including alcohol.

Recent research has begun to tease out specific contributions of ORX signaling to drug seeking, demonstrating that it is not involved under all circumstances. Thus ORX signaling is particularly influential under reinstatement induced by cues, context, or stress, whereas

maintenance of drug seeking, particularly FR1 self-administration of cocaine, or cocaine primed reinstatement is not as strongly impacted by OXR antagonism (James et al. 2017b; Mahler et al. 2014; Mahler et al. 2012b). This dichotomy may be specific for cocaine seeking as OX1R antagonism does impact maintenance of opiate and nicotine seeking (as well as alcohol seeking). These differences may reflect pharmacological profiles of different drug action (e.g., activation of dopamine neurons vs. blocking dopamine reuptake or enhancing release) or may depend on the interaction of the ORX system with separable drug-associated brain system networks. One finding that is consistent across drug types is that the ORX system is particularly involved in regulating highly-motivated seeking for many types of drugs of abuse (again, including alcohol). This can be seen during reinstatement, when response levels are inherently high, as well as when experimental demands challenge motivation for drug such as under heightened (FR5+) or increasing (progressive ratio) drug self-administration, or under binge-like conditions (Bentzley and Aston-Jones 2015; Espana et al. 2011; Espana et al. 2010; Hollander et al. 2012; Porter-Stransky et al. 2015; Schmeichel et al. 2017). In general, the overarching theme connecting ORX to drug seeking is that the ORX system is particularly involved when motivation, demand, or effort requirements are high. These, and related findings, have led to the proposal that a major function of the ORX system is motivational activation, or to energize an individual to respond to needs, challenges, or potential rewards (Mahler et al. 2014). That this fundamental process gets coopted by drugs of abuse is important in understanding what functions this system natively plays as well as for developing potential novel treatments for addiction.

One interesting outstanding question is that of whether subpopulations of ORX neurons differentially regulate reward or drug seeking vs. other aspects of emotional behavior such as stress, or play a more important function in arousal (Harris and Aston-Jones 2006). A number of studies have shown that the lateral population of ORX neurons, as opposed to those in the more dorsomedial regions, are particularly involved in reward seeking, including drug seeking. These studies have typically employed measurement of ORX neuron activation with c-Fos and have demonstrated a preferential lateral vs. medial activation of these neurons during drug seeking. In contrast, Fos activation of ORX neurons following stressful or other negative or arousing stimuli is more frequently observed in dorsomedial ORX neurons (for a thorough discussion of these studies, see (James et al. 2017b)). There are certainly exceptions to this absolute dichotomy, indicating a more complex coding structure, which may be driven by other factors such as differential efferent or afferent connectivity (Richardson and Aston-Jones 2012), though see (Gonzalez et al. 2012). Additionally, there are elements of positive and negative motivation underlying drug seeking – the absence of drug during acute or prolonged withdrawal or during reinstatement produces an aversive state that prompts motivation to acquire drug to alleviate this dysphoria (Koob 2008; Koob 2015). Thus, although there are some divisions across ORX neuron populations, these may take the form of gradations or context-specific overlap in activation. Regardless, the general finding that different populations of ORX neurons regulate separable aspects of emotion, behavior, and physiological function is important for better understanding the scope of the influence of this system.

There are a number of potential target regions where ORX projections can influence motivation for drugs of abuse. The most thoroughly studied area thus far is the VTA, where ORX, either through direct excitatory action or through regulation of glutamatergic signaling, facilitates conditioned place preference and reinstatement of drug seeking (Baimel and Borgland 2017; Borgland et al. 2006; Calipari and Espana 2012; Farahimanesh et al. 2017; Harris et al. 2005; Harris et al. 2007; James et al. 2011; Mahler et al. 2012a; Muschamp et al. 2014; Prince et al. 2015; Richardson and Aston-Jones 2012; Wang et al. 2009). The NAc is also a target of ORX projections, and ORX receptor antagonism at these targets decreases morphine CPP and reinstatement (Alizamini et al. 2017; Plaza-Zabala et al. 2013b; Qi et al. 2013; Sadeghzadeh et al. 2016), as does OX1R or OX2R antagonism in the dorsal hippocampus (Riahi et al. 2013;

Sadeghi et al. 2016). OX1R antagonism in the insular cortex reduces nicotine seeking (Hollander et al. 2008). Recently, the bed nucleus of the stria terminalis (BNST) has been implicated as a location of ORX control of stress-induced reinstatement of cocaine conditioned place preference (Conrad et al. 2012) and the ORX signaling in the CeA has been shown to underlie escalated cocaine seeking following long-access exposure (Schmeichel et al. 2017), both sites being locations where ORX may influence the intersection of stress and drug seeking due to interactions with other stress-associated systems such as dynorphin. Finally, there is a growing interest in the role of ORX release in the paraventricular nucleus of the thalamus (PVT), potentially via OX2R receptors, in cocaine seeking (James and Dayas 2013; Martin-Fardon and Boutrel 2012; Matzeu et al. 2016; Matzeu et al. 2014).

In total, it is clear from non-alcohol related research that, in addition to regulating basic physiological processes such as arousal and metabolism, the ORX system is deeply entrenched in emotion- and motivation-linked behaviors. These include food seeking, particularly for highly palatable foods, negative emotional states such as stress and fear, and motivation for drugs of abuse, which may sit at the intersection of motivation and stress. The panoply of functions subserved by this system (see more details in Section 5) demonstrates not only that it may serve as a master regulator over a wide range of behaviors, but may also indicate that disruption of the ORX system may underlie a number of diverse psychiatric diseases. Drug abuse and addiction are clearly associated with ORX disturbances, but other disorders such as depression, chronic stress and PTSD, sleep disturbances, eating disorders, and ADHD all may have dysregulated ORX signaling as an influencing factor (Chen et al. 2015; Cortese et al. 2008; James et al. 2017a; Nollet and Leman 2013; Tsujino and Sakurai 2013; Winrow and Renger 2014; Yeoh et al. 2014). The intersection between AUDs and other ORX-associated mental disease is of particular interest in the context of better understanding comorbidity and related treatment.

4. The hypocretin/orexin system and alcohol

As in the case of non-alcohol drugs of abuse, the ORX system plays an important role in regulating motivation for alcohol, particularly under circumstances where motivation for alcohol is particularly high. As noted above, previous reviews have recently discussed the role of the ORX system in alcohol use (Barson and Leibowitz 2016; Brown and Lawrence

2013; Lawrence 2010; Mahler et al. 2012b; Walker and Lawrence 2017). The section below will consider this subject with an eye towards dissecting out the system's contributions to elevated motivation in AUDs. Table 1 provides a summary of many relevant animal studies of ORX signaling in the context of alcohol use.

There has been a small number of reports relating AUDs and the ORX system in human patient populations. Blood samples taken from human patients with alcohol dependence exhibited elevated ORX in early withdrawal (Bayerlein et al. 2011; Ziolkowski et al. 2016) and these elevated levels were correlated with depression-like symptoms in that timeframe (von der Goltz et al. 2011). Thus there appears to be some association with human AUDs and the ORX system, although further work is clearly warranted.

The majority of the research associating the ORX system and alcohol use is based on studies in rats and mice. The first of these did so in alcohol preferring iP rats, demonstrating that chronic ethanol consumption increased the extent of prepro-ORX mRNA expression and that treatment with the OX1R antagonist SB-334867 (SB) decreased ethanol seeking (Lawrence et al. 2006). These two general themes – that alcohol use upregulates ORX signaling and that blockade of ORX signaling decreases alcohol use, have been extended through multiple studies to date.

Multiple studies have shown an impact of chronic alcohol use on ORX mRNA or peptide expression. Typically increases have been observed (Barson et al. 2015; Lawrence et al. 2006; Morganstern et al. 2010; Sterling et al. 2015), but in some cases decreases or no changes have been seen (Kastman et al. 2016; Morganstern et al. 2010; Olney et al. 2015; 2017). Studies have also shown alcohol-induced changes in receptor expression: increased OX1R (in mPFC), decreased OX1R (in NAc), and both increased (in PVT) and decreased (in NAc) OX2R mRNA levels (Alcaraz-Iborra et al. 2017; Barson et al. 2015). Despite potential differences across species/strain and alcohol exposure paradigms, these studies demonstrate that ORX peptide and receptor expression is dynamically regulated by alcohol exposure.

Activation of ORX neurons is also influenced by alcohol. In rats, reinstatement of alcohol self-administration elevates expression of the immediate early gene c-Fos in ORX neurons. This relationship between ORX neuron Fos activation and alcohol seeking has been demonstrated in reinstatement or renewal of alcohol seeking elicited by alcohol-associated discriminative stimuli (Dayas et al. 2008; Moorman et al. 2016), alcohol-associated contexts (Hamlin et al. 2007; Millan et al. 2010; Moorman et al. 2016), yohimbine-induced stress (Kastman et al. 2016) and, to a lesser degree, discrete alcohol-associated cues (Moorman et al. 2016). ORX neuron Fos activation was also observed after alcohol sensitization in mice (Macedo et al. 2013). In some cases, the activation of ORX neurons has been shown to be correlated with motivation (Hamlin et al. 2007; Millan et al. 2010; Moorman et al. 2016), findings which are of relevance for understanding the relationship between ORX and AUDs.

Consistent with the finding that alcohol increases ORX expression and neuronal activation, pharmacological manipulation of ORX signaling has a significant impact on alcohol seeking and use. Antagonism of the OX1R using the SB compound decreases levels of alcohol

drinking in rats (Anderson et al. 2014; Moorman and Aston-Jones 2009) and mice (Alcaraz-Iborra et al. 2017; Anderson et al. 2014; Carvajal et al. 2015; Lei et al. 2016a; Lei et al. 2016b; Lopez et al. 2016; Olney et al. 2015; 2017). OX1R antagonism also decreases operant self-administration of alcohol both on a FR3 (Lawrence et al. 2006; Lei et al. 2016b; Moorman et al. 2017; Richards et al. 2008) and progressive ratio schedule (Jupp et al. 2011a). SB treatment decreases reinstatement of alcohol seeking induced by presentation of alcohol-associated cues (Brown et al. 2016; Jupp et al. 2011b; Lawrence et al. 2006; Martin-Fardon and Weiss 2014; Moorman et al. 2017), pharmacological (yohimbine) stress (Richards et al. 2008), alcohol-associated discriminative stimuli (Jupp et al. 2011b), and infusion of neuropeptide S (Cannella et al. 2009). Alcohol conditioned place preference and sensitization are also disrupted following SB treatment (Macedo et al. 2013; Voorhees and Cunningham 2011). These results indicate that ORX signaling, likely via the OX1R, has a potent influence of alcohol seeking as characterized in multiple behavioral models.

Although the primary association between ORX and alcohol use is via the OX1R, there are reports in which OX2R signaling may be relevant as well. The dual OX1R/OX2R almorexant decreased alcohol drinking, self-administration, and progressive ratio seeking (Anderson et al. 2014; Srinivasan et al. 2012), though it is possible that these effects could be primarily driven by OX1R signaling. The OX2R antagonist TCS-OX2-29 has decreased alcohol drinking (Olney et al. 2017), operant self-administration (Brown et al. 2013), and stress-induced reinstatement (Kastman et al. 2016), though not cue-induced reinstatement (Brown et al. 2013). The OX2R antagonist JNJ-10397049 also decreased alcohol self-administration and conditioned place preference (Shoblock et al. 2011). In some cases, these effects of OX2R antagonism were efficacious when SB treatment was not, indicating either experimental differences across studies or subtle interactions between OX1R and OX2R signaling that remain elusive.

One possible explanation for different effects of OX1R vs. OX2R pharmacology could be the location of action of signaling through each receptor. Given the widespread distribution of ORX projections and receptors, it is important to characterize where in the brain ORX signaling is having an effect to promote alcohol seeking. Three main reward/motivation-associated brain areas, the VTA, the NAc, and the mPFC, are associated with ORX signaling and alcohol motivation. OX1R antagonism in the VTA decreased alcohol drinking and reinstatement (Brown et al. 2016; Olney et al. 2017), as did almorexant-induced OX1R/OX2R antagonism (Srinivasan et al. 2012). SB directed to the NAc shell reduced alcohol drinking in mice and self-administration in rats (Lei et al. 2016b), and OX2R antagonism in the NAc core but not shell reduced alcohol self-administration (Brown et al. 2013), potentially indicating selective subcircuit effects. OX1R antagonism in the mPFC reduced alcohol drinking in mice (Lei et al. 2016b) and cue-induced reinstatement in rats (Brown et al. 2016). ORX signaling in brain areas outside the VTA-PFC-NAc network also regulates alcohol seeking and use. These areas include the paraventricular nucleus of the hypothalamus and the lateral hypothalamus (Chen et al. 2014b; Schneider et al. 2007), the central amygdala (Olney et al. 2017) and BNST (Ubaldi et al. 2016), the nucleus incertus (Kastman et al. 2016), and the PVT (Barson et al. 2015; Barson et al. 2017). Thus, in addition to the canonically-identified reward-motivation system, ORX signaling regulates a number of nodes in a broad network associated with alcohol motivation and seeking.

One overarching theme in previous studies to date, and a topic of consideration for future work, is the close association between ORX function and strength of alcohol motivation. As noted above, ORX activity appears to be closely tied to the intensity of non-alcohol reward or drug seeking. This also appears to be the case for alcohol use as well. Pharmacological manipulation of the ORX system, particularly through OX1Rs, seems to have a greater effect on individuals with particularly heightened levels of alcohol-directed behaviors. OX1R antagonism decreases drinking and seeking selectively in high- vs. low-preferring rats and mice (Alcaraz-Iborra et al. 2017; Moorman and Aston-Jones 2009; Moorman et al. 2017), in binge-drinking mice (Olney et al. 2015; 2017), in strains that have been genetically selected to prefer alcohol (Anderson et al. 2014; Brown et al. 2016; Dhaher et al. 2010; Jupp et al. 2011a; Jupp et al. 2011b; Lawrence et al. 2006), in mice that have been made dependent through multiple cycles of chronic intermittent exposure to ethanol vapor (Lopez et al. 2016), and in mice that exhibit drinking that is resistant to punishment, such as quinine-adulterated alcohol (Lei et al. 2016a).

Thus, in line with studies of non-alcohol drugs of abuse described above, ORX neuron activation and ORX release is correlated with motivation for alcohol, including circumstances where it is particularly high in animal models of dependence (Lei et al. 2016a; Lopez et al. 2016). These results raise the intriguing possibility that the ORX system may be a major candidate for the target referred to in the introduction – a neural system that is closely associated with, and may even directly control, the intensity of motivation associated with AUDs. If, in fact, the ORX system is significantly dysregulated in AUDs, then returning the ORX system to a normally functioning state has the potential to limit or reverse excessive motivation directed towards alcohol, while preserving motivation for natural rewards. Given the selective impact of ORX pharmacological manipulation on high-drinking animals, it is even conceivable that ORX treatments for AUDs could transform problematically high-drinking individuals into those who are able to consume alcohol in a regulated, non-problematic fashion. Alternately, ORX pharmacotherapy could potentially facilitate abstinence by eliminating the heightened motivation for alcohol associated with AUDs.

5. Next steps: what is necessary for the ORX system to be a target for AUD treatment?

If, as suggested by the results presented above, the ORX system is a particularly important target for treating the excessive motivation, or craving, associated with alcohol use, while minimally influencing natural reward seeking, what other issues would need to be addressed? One obvious requirement would be for manipulation of the ORX system to selectively influence alcohol seeking with limited to no effects on other aspects of motivation, e.g., for natural rewards. In a number of studies this appears to be the case: OX1R antagonism decreases alcohol but not sucrose drinking in alcohol-dependent mice (Lopez et al. 2016), decreases alcohol but not saccharin drinking in mice exhibiting quinine-resistant alcohol drinking (Lei et al. 2016a), and decreases reinstatement for alcohol but not a highly-palatable glucose/saccharin solution (Martin-Fardon and Weiss 2014). OX1R antagonism also decreases responding on a progressive ratio task selectively for alcohol vs.

sucrose (Jupp et al. 2011a). OX2R antagonism reduced alcohol, but not saccharin self-administration as well, again indicating that consideration of both receptors may be important for future treatment development (Shoblock et al. 2011). There are alternate examples, where ORX receptor antagonism decreased seeking or consumption of both alcohol and natural rewards (Anderson et al. 2014; Olney et al. 2015). There are additionally cases in which ORX receptor antagonism decreases motivation for natural rewards, although it is intriguing that these effects are often seen in binge models or for highly-palatable (e.g., high sweet/high fat) rewards, and not for less-strongly motivating reinforcers (Alcaraz-Iborra et al. 2014; Borgland et al. 2009; Cason and Aston-Jones 2013; Choi et al. 2010; Clegg et al. 2002; Kay et al. 2014; Nair et al. 2008; Sharf et al. 2010). In some cases highly palatable food intake is not affected by OX1R antagonism unless motivation is elevated by chronic stress and food restriction (Piccoli et al. 2012). Thus, the effects of ORX on motivated behavior do not appear to extend broadly to all aspects of reward seeking. Instead, the system seems to primarily regulate motivation for alcohol and other drugs of abuse, as well as highly palatable natural rewards (with abuse potential), particularly in the context of binge, chronic stress, or food restriction. This has led to the proposal that this system plays a particularly salient role in compulsive, as opposed to regulated use (Lei et al. 2016a), a perspective in line with that proposed here.

There are a number of other factors that need to be considered with respect to targeting the ORX system as a treatment for compulsive alcohol motivation. One important issue that has yet to be addressed is the fact that, although the ORX system seems particularly selective for very strong levels of motivation, it also plays a role in a wide range of other behaviors and physiological functions (Flores et al. 2015; Giardino and de Lecea 2014; Graebner et al. 2015; James et al. 2017a; Kuwaki and Zhang 2012; Mahler et al. 2014; Sakurai 2014; Schone and Burdakov 2017; Sutcliffe and de Lecea 2002; Willie et al. 2001). As noted above, one of the first identified functions of the ORX system was in regulating sleep, and disruption of ORX neurons, peptides, and receptors leads to disorders such as narcolepsy with cataplexy (Lin et al. 1999; Nishino et al. 2000; Thannickal et al. 2000). Central administration of ORX or activation of ORX neurons increases overall levels of arousal (Adamantidis et al. 2007; Espana et al. 2001; Hagan et al. 1999; Sakurai 2007). Antagonism of ORX receptors, particularly OX2R, leads to increased somnolence, and OX2R mutant animals exhibit narcolepsy-like behaviors (Brisbare-Roch et al. 2007; Jacobson et al. 2017; Kummangal et al. 2013; Lin et al. 1999; Moore et al. 2014; Willie et al. 2003). The dual OX1R/OX2R antagonist suvorexant is currently approved for treating insomnia (Coleman et al. 2017; Jacobson et al. 2017).

The connection between ORX, sleep, and addiction indicates that some intersecting features may be relevant both for understanding the nature of this relationship as well as in designing future treatments for AUDs. In fact, acute and chronic alcohol exposure disrupts normal sleep, and alcohol patients with AUDs exhibit substantial sleep disruptions (Brower and Perron 2010; Colrain et al. 2014; Colrain et al. 2009; Ebrahim et al. 2013; Roehrs and Roth 2001; Sharma et al. 2014; Thakkar et al. 2015), and sleep disruption is predictive of alcohol relapse (Brower et al. 2001; Brower and Perron 2010; Drummond et al. 1998). One intriguing possibility is that pharmacological OXR antagonism, as is currently employed for insomnia, might be effective in reducing relapse in at least a number of patients with AUDs,

via a sleep-normalizing function. If, in fact, disrupted ORX signaling in AUDs patients results in both enhanced craving as well as disrupted sleep, OXR antagonism may provide a double-hit that both enhances sleep quality as well as decreases risk of alcohol relapse. This could be done via careful dosing or timing of use of dual receptor antagonists such as suvorexant, or with differential dosing with combinations of OX1R and OX2R antagonists depending on individual differences in AUD symptoms (e.g., greater OX1R for patients with enhanced craving, greater OX2R for patients with stronger sleep disturbances) (Hoyer and Jacobson 2013; Khoo and Brown 2014). The prominent role of the ORX system in multiple behaviors and physiological functions, including those disrupted in AUDs, provides interesting and novel strategies for treatment. Although this overlapping role of ORX suggests that ORX pharmacological treatment may be beneficial to sleep disorders associated with AUDs, it also warrants caution. Increased somnolence resulting from OXR antagonism could be an undesirable side effect in some patient populations. As noted above, this could potentially be addressed through careful dosing and/or selective targeting of one particular receptor subtype over another. In this regard, the observed differences between OX1R and OX2R in motivation vs. arousal, though somewhat overgeneralized, may indicate that differential treatment at each receptor might be selectively beneficial.

ORX signaling is also closely linked to emotional arousal, stress, and fear (Flores et al. 2015; Giardino and de Lecea 2014; James et al. 2017a; Johnson et al. 2012; Kuwaki and Zhang 2012), a detail which actually may facilitate ORX-based treatments for AUDs. ORX neurons project to and activate neurons in multiple targets associated with stress and anxiety such as the basolateral and central amygdala, bed nucleus of the stria terminalis, paraventricular nucleus of the hypothalamus, and locus coeruleus (Giardino and de Lecea 2014; James et al. 2017a). Panic, anxiety, and fear conditioning are associated with increased c-Fos and peptide mRNA in ORX neurons and increased ORX CSF levels (Chen et al. 2014a; Johnson et al. 2012; Johnson et al. 2010). Activation of ORX neurons and intracerebroventricular administration of ORX-A produces anxiety-like behaviors (Bonnavion et al. 2015; Suzuki et al. 2005). Receptor antagonism decreases cued and contextual fear conditioning and threat learning, decreases panic-like behaviors, and enhances extinction (Bonaventure et al. 2015; Flores et al. 2017; Flores et al. 2014; Sears et al. 2013). In addition to acute stress, chronic stress, often resulting in depression-like phenotypes, impacts the ORX system (James et al. 2017a; Nocjar et al. 2012; Nollet et al. 2011; Nollet and Leman 2013; von der Goltz et al. 2011). Chronic stress increases ORX c-Fos in medial ORX neurons (Nollet et al. 2011), but decreases overall ORX peptide levels (Nocjar et al. 2012), and CSF ORX levels are reduced in patients with clinical depression (Brundin et al. 2007). Increasing ORX levels reduces behavioral measures of despair, and the anti-depressant effects of calorie restriction are dependent on an intact ORX system, though the effects may be receptor dependent (Chung et al. 2014; Lutter et al. 2008; Scott et al. 2011). These and other findings demonstrate a clear relationship between ORX and both acute and chronic stress, anxiety, and fear. This is particularly relevant considering the fact that chronic alcohol is strongly associated with increased stress (Becker 2017; Becker et al. 2011; Koob 2014). ORX, therefore, may play a key role in connecting the enhanced alcohol motivation and the elevated stress and anxiety seen in patients with and animal models of AUD. This remains to be tested in detail, but in this case, the overlap across multiple ORX

functions may be beneficial for developing future treatments. If treatments targeting the ORX system reduce both anxiety and elevated motivation resulting from chronic alcohol use, these strategies may be more potent than selectively targeting one aspect or the other.

ORX has also been associated with cognitive functions such as attention and memory (Akbari et al. 2006; Akbari et al. 2007; Fadel and Burk 2010; Zajo et al. 2016). ORX neurons project to, and ORX receptors are found in areas associated with cognitive functions, including the prefrontal cortex, hippocampus, basal forebrain, ventral tegmental area, locus coeruleus. Disruption of the ORX system impairs attentional and spatial orienting behaviors (Boschen et al. 2009; Wheeler et al. 2014), in part through its influence over the basal forebrain acetylcholinergic system, though likely via multiple routes, such as the medial prefrontal cortex and locus coeruleus noradrenergic system. The ORX system also appears to influence memory and learning (Jaeger et al. 2002), driven in part by ORXergic influence on hippocampus neurons (Aou et al. 2003; Selbach et al. 2010; Wayner et al. 2004), though influence via the amygdala (Ardeshiri et al. 2017) and basal forebrain (Piantadosi et al. 2015) have been demonstrated as well. Activation of ORX neurons and administration of ORX enhances short-term spatial memory (Aitta-Aho et al. 2016; Deadwyler et al. 2007; Yang et al. 2013) and passive avoidance learning (Palotai et al. 2014; Telegdy and Adamik 2002), though ORX administration has also been shown to impair spatial memory on the Morris water maze (Aou et al. 2003). ORX receptor antagonism or ORX gene knockout induces spatial memory impairments (Akbari et al. 2006; Akbari et al. 2007; Dang et al. 2018; Mavanji et al. 2017). ORX neuron degeneration disrupts social memory and hippocampal synaptic plasticity (Yang et al. 2013). In general, the cognitive contributions of the ORX system have been less-well studied than its role in motivation, arousal, or anxiety. However, the work to date indicates that the contributions of ORX to cognitive functions such as attention or memory should be factored into considerations of additional impacts of treatments for AUD. In general, OXR antagonism appears to have negative effects of attention and memory in studies conducted thus far. However, a hyperactive ORX system, driving enhanced motivation for alcohol, may also contribute to cognitive deficits, such as those seen in AUDs (Le Berre et al. 2017; Oscar-Berman and Marinkovic 2007), and normalization of this system may restore cognitive function induced by chronic alcohol exposure.

Natural function of the ORX system also regulates fundamental physiological processes. ORX controls thermal regulation, cardiovascular function, respiration, metabolic homeostasis, and motor and vestibular control, all among many other functions (Carrive and Kuwaki 2017; Kuwaki 2015; Madden et al. 2012; McGregor et al. 2011; Siegel 2004; Zhang et al. 2011). Systemic ORX administration increases blood pressure, heart rate, and renal sympathetic nerve activity, and this increase can be blocked by OX1R and OX2R antagonism (Carrive and Kuwaki 2017; James et al. 2017a; Shirasaka et al. 1999). In some ways, these effects dovetail with the role of ORX in regulating arousal and stress, as elevations of cardiovascular function by social and psychological stressors are reduced by OXR antagonism (Johnson et al. 2012; Johnson et al. 2010). In a similar vein, the ORX system contributes to respiratory function. ORX administration increases respiratory frequency and volume, and at least some aspects of these increases are blocked by OXR antagonism (Carrive and Kuwaki 2017). ORX neurons are activated by decreased pH and

CO2, suggesting that they may play a role in regulating respiration or associated functions based on direct chemreception (Sunanaga et al. 2009; Williams and Burdakov 2008; Williams et al. 2007; Zhang et al. 2010). ORX system activation also increases thermogenesis and body temperature, in part due to its direct interface with brown adipose tissue (Madden et al. 2012; Oldfield et al. 2002; Tupone et al. 2011; Zhang et al. 2010), and increases locomotor activity (Kiyashchenko et al. 2001; Mileykovskiy et al. 2002; Siegel 2004).

Thus, in addition to suggesting that ORX neuron activation encodes a suite of behaviors associated with arousal, stress, and behavioral activation, these, and related findings, demonstrate that the ORX system is highly interconnected with a range of behavioral and physiological functions. Although space precludes a comprehensive discussion of the role of the ORX system in such diverse physiological processes (see references above for more details), it is clear that systemic manipulation of the ORX system as potential treatment should be considered carefully. As with the direct role of ORX in sleep/arousal, stress, and cognition, described above, potential ORX-based treatments for AUDs may impact functions in patients comorbid with disruptions of motivation for alcohol such as disrupted cardiovascular function, for example. On the other hand, due to the widespread role of the ORX system in so many non-motivation-associated physiological functions, ORX-based treatments could be problematic. Side effects of OXR manipulation could disrupt natural physiological or behavioral processes, which is an undesirable outcome that limits efficacy of and patient adherence to novel medications.

This concern is potentially addressable with further information on specific ORX targets. Because ORX receptors and projections are so widespread, global ORX modulation will result in a host of potential disruptions. However, if we can identify the receptors and brain areas associated specifically with the pathologically enhanced motivation driving compulsive alcohol use, we may be able to specifically attack this disruption while leaving other aspects of ORX signaling intact. Alternately, AUDs may be driven by a broader disruption of ORX signaling in general, in which case a more global treatment strategy is actually desirable. Drug abuse and addiction are clearly associated with ORX disturbances, but other disorders such as depression, chronic stress and PTSD, sleep disturbances, eating disorders, and ADHD all may have dysregulated ORX signaling as an influencing factor (Chen et al. 2015; Cortese et al. 2008; James et al. 2017a; Nocjar et al. 2012; Nollet and Leman 2013; Tsujino and Sakurai 2013; Winrow and Renger 2014; Yeoh et al. 2014). If, in fact treatment of a globally disrupted ORX system could result in normalized reward motivation as well as potential amelioration of additional co-occurring disorders, there is additional impetus focus our attention to this system (Chieffi et al. 2017).

Another issue to consider for future study is which aspect of the ORX system to target. Research to date has primarily focused on pharmacological manipulation of the OX1R or OX2R or, in some cases (such as with suvorexant) both receptors together. This is likely an optimal strategy – defining the contributions of OX1R vs. OX2R signaling at discrete neural locations to behavior. Careful dose regulation of OX1R- and OX2R-targeting compounds might result in an optimized treatment strategy that specifically reduces AUD-associated behaviors while minimally impacting natural physiological function. Although this strategy

has not been significantly pursued to date, identification of the behavioral and physiological consequences of a range of OXR antagonist doses may provide essential information about optimal dose windows for disease treatment with minimal side effects. This parametric treatment strategy might also be valuable for treating AUDs that co-occur with other behavioral or physiological disorders, such as sleep disruption or elevated anxiety.

Another potential target may be the ORX neurons themselves. Although somewhat more speculative a stretegy than currently available techniques permit in the clinic, AUDs and related disorders may stem from disrupted ORX neural function. In this case, characterization of normal and pathological ORX neuronal function will be critical for future treatment. This issue is particularly salient given the fact that ORX neurons co-express multiple neurotransmitters and neuromodulators. Of particular interest with respect to AUDs is co-expression of the peptide dynorphin, which also plays a critical role in the regulation of alcohol use and abuse (Anderson and Becker 2017). Recent work is beginning to identify the unique contributions of ORX vs. dynorphin released from “ORX” neurons, and has shown that these two peptides play a delicate excitatory/inhibitory balancing act in modulating motivation-associated brain areas such as the VTA and PVT (Baimel and Borgland 2017; Baimel et al. 2017; Matzeu et al. 2017; Muschamp et al. 2014). The interaction of these systems in the context of AUDs is an important future line of research given their close association. Other co-expressed signaling molecules such as glutamate (Harthoorn et al. 2005; Henny et al. 2010; Rosin et al. 2003; Schone and Burdakov 2012; Torrealba et al. 2003), galanin (Hakansson et al. 1999), prolactin (Risold et al. 1999), neuronal activity-regulated pentraxin (Crocker et al. 2005; Reti et al. 2002), and neurotensin (Furutani et al. 2013), among others, will require similar interrogation in order to develop a comprehensive perspective on how these multifaceted neurons regulate such a wide range of normal and disease functions. In general, we are presented with a complex challenge with respect to the ORX system. There is clearly a close association between some aspect of the ORX system and AUDs, and the possibility of targeting this system for treatment is enticing. However, the complexity of the system as a whole, including its component receptors and neurons, as well as the fact that this system is so broadly and diversely influential, indicates that more work needs to be done to identify the specifics of this system as a potential target for treatment.

6. Conclusions

Optimal treatments for AUDs would isolate the specific disease-associated neural disruption and correct it, while leaving other aspects of natural behaviors intact. Identifying what underlies the transition from regulated alcohol use to compulsive, excessively-motivated alcohol seeking would allow the design of treatment strategies that are free from side effects and facilitate treatment maintenance. The ORX system provides a potential avenue for the design of next-generation treatments that preserve normal behavioral function while potentially dampening uncontrollable urges for alcohol. As discussed, the ORX system does not simply regulate reward seeking, but appears to be selective for enhanced motivation, whether that is through salience of reward stimuli, innate predispositions, or development of dependence that elevates the need for continued alcohol use. In this regard, this system offers significant potential for future investigation and development. The participation of the

ORX system in a wide range of behaviors is both a blessing and a curse. AUDs do not only result from disruptions in reward-seeking. There are significant contributions of elevated stress, decreased hedonic state, and cognitive disruption, making the AUDs, and addictions in general, complex, multifaceted diseases. A focus on the ORX system may be particularly beneficial in this capacity. The prominent role of the ORX system in stress and anxiety, for example (Flores et al. 2015; Giardino and de Lecea 2014; James et al. 2017a; Johnson et al. 2012; Kuwaki and Zhang 2012), in addition to its role in motivated behavior, may place this system at the precise intersection of behaviors disrupted in AUDs. In effect, treating the ORX system may result in a multiple hit strategy, decreasing stress, diminishing craving, potentially improving sleep, and providing other health benefits. The downside to the breadth of ORX contributions to normal behavior is that a global ORX receptor antagonist strategy is likely insufficiently precise to alleviate AUDs without side effects. In this regard, future research, as described in the sections above, will enhance our understanding of how the ORX system selectively contributes to AUDs, providing avenues for treatments that include relevant dimensions (motivation, stress, etc.), while excluding others (metabolism, temperature, etc.). There is much work to be done to identify the most relevant targets – be they specific populations of neurons, specific receptors, or specific brain areas receiving ORX projections. However, the tantalizing possibility of treatments optimized to selectively excise the disease aspects of AUDs while preserving normal emotional and motivated behaviors is sufficient incentive to continue investigation of this system.

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Table 1

Animal studies of ORX and Alcohol

Reference	Cellular measurements (mRNA, Fos, etc.)	Receptor pharmacology	Anatomical targets	Effects on or influence of elevated motivation	Non-cannonical (effects e.g., stronger OXR2)
Olney et al. 2017	+	+	+	+	+
Jupp et al. 2011b	+	+	+	+	−
Alcaraz-Iborra et al. 2017	+	+	+	+	−
Kastman et al. 2016	+	+	+	−	−
Lei et al. 2016b	+	+	+	−	−
Barson et al. 2017	+	+	+	−	−
Lawrence et al. 2006	+	+	−	+	−
Olney et al. 2015	+	+	−	+	−
Macedo et al. 2013	+	+	−	−	−
Chen et al. 2014	+	+	−	−	−
Carvajal et al. 2015	+	+	−	−	−
Barson et al. 2015	+	−	+	+	−
Hamlin et al. 2007	+	−	−	+	−
Morganstern et al. 2010	+	−	−	+	−
Pickering et al. 2007	+	−	−	−	−
Dayas et al. 2008	+	−	−	−	−
Millan et al. 2010	+	−	−	−	−
Chang et al. 2012	+	−	−	−	−
Sterling et al. 2015	+	−	−	−	−
Moorman et al. 2016	+	−	−	−	−
Sterling et al. 2016	+	−	−	−	−
Brown et al. 2013	−	+	+	+	+
Brown et al. 2016	−	+	+	+	−
Ubaldi et al. 2016	−	+	+	−	+
Schneider et al. 2007	−	+	+	−	−
Srinivasan et al. 2012	−	+	+	−	−
Anderson et al. 2014	−	+	−	+	+
Moorman and Aston-Jones 2009	−	+	−	+	−

Reference	Cellular measurements (mRNA, Fos, etc.)	Receptor pharmacology	Anatomical targets	Effects on or influence of elevated motivation	Non-cannonical (effects e.g., stronger OXR2)
Dhaher et al. 2010	−	+	−	+	−
Jupp et al. 2011a	−	+	−	+	−
Lei et al. 2016a	−	+	−	+	−
Lopez et al. 2016	−	+	−	+	−
Moorman et al. 2017	−	+	−	+	−
Shoblock et al. 2011	−	+	−	−	+
Voorhees and Cunningham 2011	−	+	−	−	+
Prasad and McNally 2014	−	+	−	−	+
Richards et al. 2008	−	+	−	−	−
Cannella et al. 2009	−	+	−	−	−
Martin-Fardon and Weiss 2014	−	+	−	−	−

Table summarizes almost all publications related to the orexin/hypocretin system and alcohol use or seeking in animals as of publication (with apologies for any overlooked manuscripts). Studies are categorized with a + or − based on whether or not they used techniques or reported findings described in the top row. Note that studies can have + in multiple categories. Studies including cellular measurements (mRNA, Fos, etc.) received a + in the first column. Studies including receptor pharmacology received a + in the second column. Studies that probed ORX effects in target regions received a + in the third column. Studies in which the effects (cellular- or receptor-based) were associated with elevated motivation received a + in the fourth column. Finally, whereas most studies demonstrated a role for OX1R in highly-motivated alcohol seeking, studies that demonstrated alternate effects (such as a role for OX2R signaling in alcohol use) are noted with a + in the fifth column. Studies are sorted in order of findings (cellular measurements, then receptor pharmacology, etc.) in order to facilitate identifications of studies using specific techniques or demonstrating specific phenomena.

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