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Orexin-1 receptor blockade suppresses compulsive-like alcohol drinking in mice

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ABSTRACT

Addiction is promoted by pathological motivation for addictive substances, and, despite extensive efforts, alcohol use disorders (AUDs) continue to extract a very high social, physical, and economic toll. Compulsive drinking of alcohol, where consumption persists even when alcohol is paired with negative consequences, is considered a particular obstacle for treating AUDs. Aversion-resistant alcohol intake in rodents, e.g. where rodents drink even when alcohol is paired with the bitter tastant quinine, has been considered to model some compulsive aspects of human alcohol consumption. However, the critical mechanisms that drive compulsive-like drinking are only beginning to be identified. The neuropeptide orexin has been linked to high motivation for cocaine, preferred foods, and alcohol. Thus, we investigated the role of orexin receptors in compulsive-like alcohol drinking, where C57BL/6 mice had 2-hr daily access to 15% alcohol with or without quinine (100 μM). We found that systemic administration of the widely used selective orexin-1 receptor (OX1R) blocker, SB-334867 (SB), significantly reduced compulsive-like consumption at doses lower than those reported to reduce quinine-free alcohol intake. The dose of 3-mg/kg SB, in particular, suppressed only compulsive-like drinking. Furthermore, SB did not reduce concurrent water intake during the alcohol drinking sessions, and did not alter saccharin + quinine consumption. In addition, the OX2R antagonist TCS-OX2-29 (3 or 10 mg/kg) did not alter intake of alcohol with or without quinine. Together, our results suggest that OX1R signaling is particularly important for promoting compulsive-like alcohol drinking, and that OX1Rs might represent a novel therapy to counteract compulsive aspects of human AUDs.

1. Introduction

Addiction to alcohol and other abused substances is typified by enhanced, and often pathological, motivation for the substance (Koob and Volkow, 2010; Larimer et al., 1999; Sinha, 2009). Despite decades of research, alcohol use disorders (AUDs) remain a major problem with a very high social, personal, and economic toll (Blincoe et al., 2002; Bouchery et al., 2011; CDC, 2014; Harwood et al., 1998; Hingson et al., 2005; Mokdad et al., 2004; Sacks et al., 2013; SAMHSA, 2014), especially due to a lack of effective pharmacotherapies (Spanagel, 2009; World Health Organization, 2014).

Compulsive alcohol intake, where drinking persists despite the knowledge of associated negative consequences, is considered a major obstacle when treating AUDs (Anton, 2000; Anton et al., 1996; Hopf and Lesscher, 2014; Koob and Volkow, 2010; Larimer et al., 1999; Modell et al., 1992; Naqvi et al., 2014; Sinha, 2009; Tiffany and Conklin, 2000). Therefore, to effectively reduce the impact of AUDs, it is critical to understand the mechanisms that drive this consequence-resistant, compulsive-like alcohol consumption. In this regard, voluntary drinking paradigms, where animals will drink despite pairing the alcohol with an aversive consequence (such as bitter-tasting quinine or foot-shock), have been utilized to model some compulsive-like aspects of AUDS in humans (Hopf et al., 2010; Hopf and Lesscher, 2014; Lesscher et al., 2010; Loi et al., 2010; Marchant et al., 2013; Spanagel and Holter, 1999; Spoelder et al., 2015; Vengeliene et al., 2009). In addition, we previously demonstrated that a similar corticoaccumbens circuit promotes both shock-resistant and quinine-resistant alcohol drinking (Seif et al., 2013). Since shock-resistant intake is considered to have face and predictive validity for compulsive intake in humans, e.g. for cocaine (Everitt and Robbins, 2005; Hopf and

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Lesscher, 2014; Lesscher and Vanderschuren, 2012), the observation of a similar circuit for shock- and quinine-resistant alcohol drinking (Seif et al., 2013) validates the use of alcohol-quinine drinking to model compulsive-like drives for alcohol (Hopf et al., 2010; Hopf and Lesscher, 2014; Lesscher et al., 2010; Loi et al., 2010; Marchant et al., 2013; Spanagel and Holter, 1999; Spoelder et al., 2015; Vengeliene et al., 2009). For the present studies, we utilized a recently developed compulsive-like drinking model in mice, modified from Lesscher et al. (2010) where aversion-resistant alcohol drinking is apparent after only a single protracted session of alcohol-only consumption, and with binge-like blood alcohol levels (Lei et al., in press). This is in contrast to studies in outbred rats, where months of alcohol drinking are required to develop compulsive-like alcohol drinking patterns (Hopf et al., 2010; Spanagel and Holter, 1999), and allows more rapid investigation into the mechanisms contributing to compulsive-like alcohol drinking.

Unfortunately, the central signaling mechanisms and circuits that promote compulsive-like alcohol consumption have been understudied until very recently (Barbier et al., 2015; Lesscher et al., 2012; Seif et al., 2013, 2015; Vendruscolo et al., 2012; Warnault et al., 2016). Here, we focus in particular on the importance of orexin (OX) receptors (OXRs) in promoting compulsive-like alcohol consumption. Over the years, OX – a neuropeptide synthesized in a subgroup of lateral hypothalamic cells which have projections throughout the brain – has been identified to play a role in a number of homeostatic and regulatory behaviors, including feeding, sleep-wake cycle, as well as emotional and neuroendocrine regulation (Brown et al., 2015a; Li et al., 2016; Mahler et al., 2014). OXRs have also been addressed in many studies of drugs of abuse, including cocaine, opioids, nicotine and alcohol (Barson and Leibowitz, 2016; Boutrel et al., 2013; Mahler et al., 2012, 2014). There are two subtypes of OX receptors, OX1R and OX2R (Mahler et al., 2012). Both OX1Rs and OX2Rs can contribute to promoting alcohol drinking (Mahler et al., 2012), although extant studies suggest a stronger overall role for OX1R signaling during addictive behaviors relative to OX2Rs (Baimel et al., 2014; Barson et al., 2014; Brown et al., 2015b; Mahler et al., 2014; Moorman and Aston-Jones, 2009; but see Anderson et al., 2014; Brown et al., 2013). OX1Rs in particular appear to play a greater role in behaviors directed towards highly salient reinforcers, such as cocaine and high fat diet (Baimel et al., 2014; Borgland et al., 2009; Cason et al., 2010; Mahler et al., 2014), higher alcohol preference and intake (Moorman and Aston-Jones, 2009), and increased alcohol drinking in dependent mice (Lopez et al., 2016).

Since OX1Rs play a preferential role in pursuit of highly motivating substances, and compulsive-like intake represents a state of high motivation (willingness to drink alcohol despite the strong negative consequences) (Hopf et al., 2010; Hopf and Lesscher, 2014; Naqvi et al., 2014; Seif et al., 2013, 2015; Tiffany and Conklin, 2000), we hypothesized that mice engaging in compulsive-like intake would be more sensitive to the effects of OX1Rs inhibition than mice drinking regular, quinine-free alcohol. OX and OX1R signaling could represent an important and interesting mechanism that promotes compulsive-like alcohol drinking, with possible utility for clinical and therapeutic settings (Khoo and Brown, 2014; Li et al., 2016).

2. Methods

2.1. Animals

Male C57BL/6 mice, 7–8-wks of age (Jackson Laboratories) were single-housed on a 12:12 light:dark cycle with the lights off at 10:00 a.m. Food and water were available *ad libitum*. All procedures followed the Guide for Care and Use of Laboratory Animals provided by the National Institutes of Health, and approval of the Institutional Animal Care and Use Committee of UCSF.

2.2. Limited daily access (LDA) two-bottle choice to alcohol or quinine adulterated alcohol

Our drinking model was as reported in Lei et al. (in press), where mice consistently engaged in alcohol drinking despite pairing with the aversive consequence of bitter-tasting quinine. Mice were acclimated to housing conditions for approximately 2-wks. Afterwards, mice were first given one 24-hr session of drinking of alcohol-only under two-bottle choice access (one bottle with 15% alcohol in water, one bottle with water), and then a 24-hr withdrawal period. Thereafter, mice drank under a Limited Daily Access (LDA) paradigm, with 2-hr/day, 5-d/wk of two-bottle choice (Fig. 1). Each day, access to alcohol began approximately 3-hr into the dark cycle. To test for compulsive-like drinking, mice were then divided into two groups: (1) those drinking alcohol without quinine (Alc) and (2) those drinking alcohol adulterated with quinine (100 μM; AlcQ). To test whether the effects of the selective OX1R antagonist, SB-334867, were specific to alcohol-quinine, a separate group of mice were given the same drinking schedule, but instead of alcohol-quinine, in each drinking session they were presented with a 0.05% saccharin solution adulterated with 100 μM quinine (SacQ), a taste which alcohol has been reported to reflect (Goodwin and Amit, 1998). In order to account for spillage, bottles containing water, alcohol or saccharin were placed onto an empty cage on the same animal racks as the experimental subjects. Furthermore, in order to control for side preference, the bottle placements of the solutions were alternated between each drinking session.

2.3. Drugs

After 3-wk of LDA, mice began to be handled for habituation and systemic injections. The selective OX1R antagonist, SB-334867 (SB, Tocris), was dissolved in 2% DMSO in 25% (2-Hydroxypropyl)-β-cyclodextrin (Sigma) and 0.9% saline; the OX2R antagonist TCS-OX2-29 (TCS, Tocris) (Huang et al., 2010; Plaza-Zabala et al., 2013) was dissolved in 0.9% saline. Animals were injected, intraperitoneally (i.p.), 30-min prior to the drinking sessions. Subjects received either 0, 0.3, 1, 3 or 10-mg/kg-body-weight of SB, or 3 or 10-mg/kg-body-weight of TCS at a volume of 10-ml/kg (similar to previously

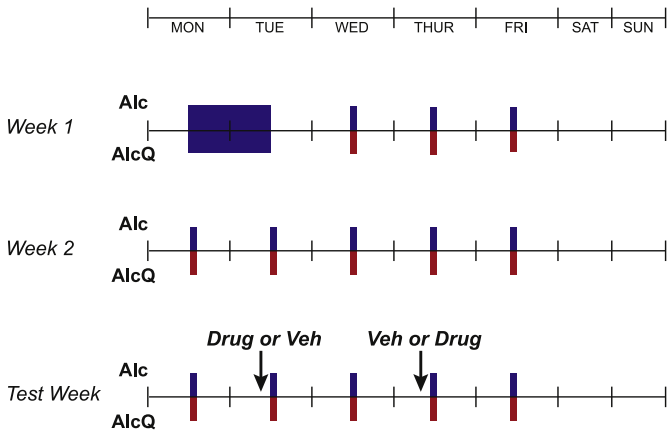

Fig. 1. Timeline of mouse drinking paradigm. See Methods for details. Briefly, mice initially had 24-hr two-bottle choice access to alcohol-only (15% v/v) in one bottle and water in the other bottle, followed by subsequent limited daily access (LDA) two-bottle drinking of either alcohol-only (blue) or alcohol-quinine (red) for 2-hr/day, 5-d/wk.