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The Role of Oxytocin in Alcohol and Drug Abuse

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Abstract

The neuropeptide oxytocin (OXT) plays a key role in adaptive processes associated with reward, tolerance, memory and stress responses. Through interactions with brain reward and stress systems, OXT is known to play a role in several neuropsychiatric disorders, particularly those that involve altered social integration, such as alcohol and drug addiction (Heilig et al., 2016). As such, there is growing interest in the oxytocin system as a potential therapeutic target for the treatment of alcohol and substance use disorders. Accumulating preclinical evidence suggests that administration of OXT influences the development of tolerance, sensitization and withdrawal symptoms, and modulates numerous alcohol/drug-seeking and alcohol/drug-taking behaviors. Further, there is some evidence to suggest that OXT may help to reverse neuroadaptations that occur as a result of chronic alcohol or drug exposure. To date, there have been only a handful of clinical studies conducted in alcohol and drug dependent populations. This review summarizes the preclinical and clinical literature on the effects of OXT administration on alcohol- and drug-related behaviors. In addition, we discuss OXT interactions with the hypothalamic-pituitary-adrenal axis and multiple neurotransmitter systems within addiction circuitry.

Keywords

Oxytocin; Addiction; Substance Use Disorder; Drug; Alcohol; Relapse

1. Introduction

Classically, the neuropeptide oxytocin (OXT) has been associated with maternal behaviors such as parturition, uterine contractions, and suckling (Gimpl and Fahrenholz, 2001). Aside from its known hormonal role in parturition and maternal behaviors, OXT also regulates a number of behaviors that involve social interactions (e.g., pair-bonding, social reward processing, aggression) and nonsocial behaviors, including anxiety and stress responses (Baskerville and Douglas, 2010, Burkett and Young, 2012, Neumann and Landgraf, 2012). Further, through interactions with brain reward and stress systems, OXT is known to play a

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role in several neuropsychiatric disorders, including alcohol and drug addiction. It has been hypothesized that drug-mediated and social reward signals compete within brain reward circuity (Leong et al., 2018, Insel, 2003, Buisman-Pijlman et al., 2014). There is evidence to suggest that OXT may enable the rewarding effects of prosocial behavior at the expense of drug-related rewards (Sarnyai and Kovács, 2014, Thompson et al., 2007, Leong et al., 2018), though the mechanism by which this occurs is still under investigation. Further, OXT has been shown to have potent anxiolytic properties and can reduce HPA-axis reactivity following acute stress (Dabrowska et al., 2011, Slattery and Neumann, 2010, Windle et al., 2006). Understandably, the ability of this nonapeptide to modulate both stress and motivational processes has generated growing interest in its potential as a much-needed therapeutic target for the treatment of alcohol and other substance use disorders (Bowen and Neumann, 2017, Lee et al., 2016, McGregor and Bowen, 2012).

This chronic relapsing disorder involves a cyclic behavioral pattern that is initially driven primarily by impulsive, reward-seeking that, overtime, transitions to compulsive alcohol/drug taking largely driven by behavior aimed at reducing negative affect and anxiety (Koob and Volkow, 2010, Koob and Volkow, 2016). The transition in some users in response to alcohol and/or drug use is mediated by neuroplastic changes in brain reward-, stress- and executive functioning systems (Kalivas and Volkow, 2005, Koob, 2008, Koob and Volkow, 2010, Koob and Volkow, 2016). Oxytocin may be beneficial in the treatment of alcohol and substance use disorders through modulation of adaptive processes associated with reward, tolerance, memory and stress responses (Lee et al., 2016). Convergent pathways within the mesocortiolimbic dopamine systems involved in the processing of motivationally relevant stimuli not only have important ramifications for social and maternal behaviors, but they also may have significant influence on the rewarding aspects of alcohol and other substances of abuse (Baskerville and Douglas, 2010, Burkett and Young, 2012). Oxytocin is also known to exert potent anti-stress and anxiolytic effects (Jurek et al., 2015, Peters et al., 2014, Slattery and Neumann, 2010) through interaction with the HPA-axis and extra-hypothalamic stress-related brain regions, thereby enabling OXT to contribute to the regulation of negative affect and stress-related behaviors relevant to addiction. The role of OXT in various neurobehavioral and neurochemical aspects of alcohol and drug addiction are described below. Additionally, current evidence pointing to the therapeutic potential for OXT as a treatment for alcohol and substance use disorders is presented as well.

2. Structure and Function of the Endogenous Oxytocin System

Oxytocin is nonapeptide that exerts a wide spectrum of central and peripheral effects, ranging from the modulation of stress and neuroendocrine response to the establishment of complex social behaviors (Gimpl and Fahrenholz, 2001). Oxytocin is synthesized in magnocellular neurons of the mammalian hypothalamus, specifically within the bilateral paraventricular nucleus (PVN), supraoptic nucleus (SON), and accessory magnocellular (AN) nuclei (Jurek and Neumann, 2018, Ludwig and Leng, 2006). These neurons possess major axonal projections to the neurohypophysis by which OXT is released into the blood stream for peripheral distribution (Leng and Ludwig, 2016, Quirin et al., 2011). Oxytocin is released from the posterior pituitary in response to a variety of stimuli including sucking, parturition and stress (Gimpl and Fahrenholz, 2001). Further, OXT may also be synthesized

in peripheral tissue such as sexual organs, placenta, corpus luteum and heart for local release or release into the bloodstream (Gimpl and Fahrenholz, 2001).

In the brain, OXT is not only released from the posterior pituitary, but these magnocellular neurons of the SON and PVN also possess axon collaterals that extend long range projections to various forebrain regions, including the prefrontal cortex (PFC), anterior olfactory nucleus, nucleus accumbens (NAc), lateral septum (LS), hippocampus (HIPP), bed nucleus of the stria terminalis (BNST) and amygdala (Stoop, 2012). Oxytocin synthesis also occurs in smaller parvocellular neurons of the PVN and, to a lesser degree, in selective extra-hypothalamic neurons (Jurek and Neumann, 2018). These neurons are distinct from magnocellular populations in that they do not release OXT into the bloodstream (Knobloch and Grinevich, 2014). Parvocellular OXT neurons project mainly to the brainstem and spinal cord where they synapse to effect autonomic functions, pain regulation and analgesia (Eliava et al., 2016).

Currently, there has been only one OXT receptor identified (Gimpl and Fahrenholz, 2001), and it is located in abundance throughout both central and peripheral systems. The OXT receptor (OXTR) is a member of the family of the rhodopsin-type 1 G protein-coupled receptor (GPCR) family and, together with three vasopressin receptor subtypes (V1a, V1b and V2), forms a subfamily of structurally related receptors (Devost et al., 2008). Centrally, OXTRs are typically abundant in brain areas that regulate social and emotional behaviors and reward, such as PFC, ventral tegmental area (VTA), NAc, caudate putamen (CPu), lateral septum (LS), hippocampus, hypothalamus, ventral pallidum (VP), bed nucleus of the stria terminalis (BNST), amygdala, and brainstem (Freeman and Young, 2016). However, expression of OXTR within the CNS is highly variable, even within species and expression patterns appear to be related to a number of factors including gonadal hormones, early life experience as well as functional and adaptive patterns of sociality and aggression (Dumais and Veenema, 2016, Carter, 2017). Sex-related differences in OXTR binding density have been identified in multiple brain regions (NAc, dorsal CPu, LS, BNST, hippocampus, amygdala, hypothalamus in rats; (Dumais et al., 2013) though this appears to be highly species-dependent as some rodent species (voles, C57BL/6J mice; (Bales et al., 2007, Smeltzer et al., 2006, Hammock and Levitt, 2013) and humans (Loup et al., 1991) show limited to no sex-related differences in brain OXTR expression (Dumais and Veenema, 2016). However, many of these studies only analyzed OXTR in a few brain regions, highlighting a need for more comprehensive analysis to determine sex-related differences in OXTR across species.

The wide distribution of receptors underlies the ability of OXT to exert a wide array of behavioral effects, including regulation of learning and memory processes, stress response, emotionality/mood, and social and reward related behaviors (Gimpl and Fahrenholz, 2001). The OXTR is diverse in its signaling pathways (many of which remain unexplored) and the precise mechanisms by which OXT exerts multiple biological actions have not been fully established (Devost et al., 2008). Nonetheless, OXT appears to be functionally coupled to the Gq/11- mediated pathway, stimulating phospholipase C (PLC) to induce increased intracellular calcium and inositol trisphosphate production (InsP3) (Vrachnis et al., 2011). However, depending on brain area and concentration, OXT also promotes activation of Gi

and Go coupled signaling cascades (Busnelli et al., 2012). While the precise role for these OXTR signaling pathways within the brain is relatively unknown, the promiscuity of OXTR (coupling to Gq or Gi/Go) most likely results in opposite effects on cell excitability (Gravati et al., 2010). One possible hypothesis is that the local concentration reached by OXT may engage different signaling pathways to allow for more finely tuned signaling mechanisms and behavioral responses (Grinevich et al., 2016). Further, due to high structural homology OXT can also bind to and activate the related vasopressin receptor subtypes (V1a, V1b and V2) (Knobloch and Grinevich, 2014). Under some conditions, this may constitute alternative targets for OXT, especially at pharmacological concentrations and in brain regions that have little or no OXTR expression (Grinevich et al., 2016).

3. Oxytocin Signaling is Altered by Alcohol and Drug Exposure

Numerous studies have reported altered OXT signaling in the brain following both acute and chronic exposure to alcohol and drugs. For example, studies in rodents have shown that chronic exposure to nicotine, methamphetamine, cocaine, and morphine generally result in an upregulation of OXTR binding and decrease in OXT peptide content in various brain regions (Georgiou et al., 2015, Zanos et al., 2016, Zanos et al., 2014). Repeated exposure to cocaine in rats produced a reduction in OXT plasma concentrations, accompanied by reduced OXT content in hypothalamus and hippocampus, which may reflect decreased OXT synthesis and release (Sarnyai et al., 1992). Chronic methamphetamine administration produced an upregulation in OXT receptor density in the amygdala and hypothalamus (Zanos et al., 2014). Marked alterations in OXT peptide and/or synthesis have also been reported following opiate administration. In mice, repeated exposure to morphine resulted in decreased OXT levels in the hippocampus (Kovacs et al., 1987). Chronic morphine treatment in rats produced region-specific alterations in brain OXT expression, with decreased *Oxt* mRNA in the hypothalamus (SON) and NAc and increased mRNA expression in the VTA and locus coeruleus (You et al., 2000). Further, withdrawal from morphine induced a decrease in hypothalamic OXT peptide levels and concomitant increase of OXTR binding in the lateral septum (LS) and amygdala (Zanos et al., 2014). Similarly, naloxone-precipitated morphine withdrawal increased plasma OXT levels, as well as the firing rate of oxytocinergic neurons in the SON of chronically morphine treated, lactating rats (Bicknell et al., 1988), as well as increased expression of *Fos* protein within the SON (Johnstone et al., 2000) and OXT mRNA levels within the PVN (Laorden et al., 1998) in opiate dependent rats.

Results from human postmortem studies shed some light on the effects of chronic alcohol on the OXT system. In male subjects with alcohol use disorder, OXT peptide immunoreactivity was decreased in both the SON and PVN compared to controls (Sivukhina et al., 2006). More recently, Lee et al. (2017b) reported a significant increase in *Oxt* mRNA in the PFC of human post-mortem AUD subjects compared to controls. In addition, the authors reported hypertrophy of OXT producing neurons in the hypothalamus in AUD patients, in concordance with previous evidence to suggesting that this effect is attributable to chronic alcohol exposure (Madeira et al., 1993). Congruent with these findings, a loss of hypothalamic OXT neurons after prolonged alcohol intake has been reported in animal studies (Silva et al., 2002, Stevenson et al., 2017b). Following repeated cycles of chronic

intermittent alcohol vapor exposure to induce dependence in rats, Hansson et al. (2018) reported that *Oxt* mRNA levels were reduced in the NAc following acute alcohol exposure as well as during early withdrawal, but increased after prolonged (3 weeks) abstinence, suggesting dynamic dependence-related neuroadaptation of the OXT system (Hansson et al., 2018). Additionally, after 3 weeks of abstinence, alcohol-dependent rats showed increases in OXT receptor mRNA and protein levels in PFC, striatal, amygdala and hippocampal regions, and a reduction in OXT mRNA and peptide expression in hypothalamic nuclei (Hansson et al., 2018).

Overall, drug and alcohol exposure appear to produce compensatory neuroadaptive changes in the endogenous OXT system in brain regions specifically involved in the addiction process, though these changes appear to be drug- and possibly species-specific. Impaired functioning of the brain OXT system is likely to contribute to dysfunctional social-, reward-, and stress-related behaviors (Bowen and Neumann, 2017). Therefore, administration of OXT may be beneficial in restoring behavior by compensating, at least in part, for abnormalities in the brain OXT system due to alcohol or drug exposure.

4. Oxytocin Effects of Alcohol/Drug on Self-Administration and Reward

A large number of preclinical studies have investigated the effect of OXT on various alcohol/drug-induced behaviors throughout the phases of addiction pathology (Lee et al., 2016, Lee and Weerts, 2016, Leong et al., 2018). During the early stage of addiction, alcohol/drug use is motivated primarily by the acute reinforcing effects (“positive”) of a substance, mediated by mesocortiolimbic dopamine systems (Koob, 2013a, Koob and Le Moal, 2001). All addictive drugs have been shown to directly or indirectly active dopaminergic neurons originating in the VTA. These projections converge on targets in the limbic forebrain, including the NAc which appears to be the primary region assigning importance to the drug experience (Koob and Volkow, 2010, Wise, 1998). Activation of dopamine systems by alcohol or drugs of abuse sensitizes the reward system and attaches incentive salience to both the substance and drug-related stimuli to drive goal-directed (impulsive) behavior (Uhart and Wand, 2009). The transition from controlled to compulsive drug taking has been associated with a shift in the involvement of NAc to the dorsal striatum that is associated with habit formation (Everitt and Robbins, 2013, Volkow and Morales, 2015).

Accumulating evidence suggests a clear role for the oxytocinergic system in the acute reinforcing effects of drugs and alcohol (Lee et al., 2016, Lee and Weerts, 2016, Leong et al., 2018). With respect to self-administration behavior in preclinical models, administration of exogenous OXT has been shown to effectively decrease both acquisition and maintenance of alcohol (Bowen et al., 2011, MacFadyen et al., 2016, Peters et al., 2013, Peters et al., 2017, Stevenson et al., 2017a), heroin (Ibragimov et al., 1987, Kovacs et al., 1985), cocaine (Leong et al., 2017, Leong et al., 2016, Sarnyai and Kovacs, 1994, Zhou et al., 2014), methamphetamine (Carson et al., 2010a, Carson et al., 2010b, Qi et al., 2009), and nicotine (Lee et al., 2017a, Manbeck et al., 2014). However, the specific effect of OXT on drug-taking behavior appears to be dose-, drug-, use history-, and possibly species-dependent. For example, early studies showed that peripherally administered OXT slightly increased heroin self-administration in rats (Ree and Wied, 1977). In support of this finding, central OXT

administration did not prevent the acquisition of morphine-conditioned place preference (CPP), and instead, increased the expression of CPP in rats (Moaddab et al., 2015). In contrast, systemically administered OXT decreased both the acquisition and maintenance of heroin self-administration (Kovacs et al., 1985), and inhibited heroin self-administration in heroin-tolerant, but not heroin-naïve rats and mice (Kovacs et al., 1985, Kovács and Van Ree, 1985). Further, site-specific micro infusion of OXT into the NAc or ventral hippocampus attenuated heroin self-administration in heroin-dependent rats, and this effect was prevented by OXT receptor blockade (Ibragimov et al., 1987). However, it is important to note that only a single, low dose of heroin was tested in these early studies making it difficult to determine OXT effect on opioids is inhibiting or potentiating. Future studies are necessary to determine dose-response information.

Systemic injection of OXT has been demonstrated to dose-dependently reduce cocaine self-administration using operant conditions procedures across varying schedules of reinforcement in male (Zhou et al., 2014) and female (Leong et al., 2016) rats. Additionally, using a model of behavioral economics, Bentzley et al., (2014) demonstrated that OXT administration reduced the demand and suppressed motivation for cocaine in male rats with a history of cocaine self-administration. Systemic OXT administration (0.3 and 1mg/kg; ip.) reduced active lever responding and methamphetamine infusions using operant self-administration procedures and reduced motivation to respond for meth on a progressive ratio schedule (Carson et al., 2010a, Carson et al., 2010b). Additionally, central administration (icv) infusions of oxytocin (2.5ug) impaired the acquisition of methamphetamine-induced conditioned-place preference (Qi et al., 2009). However, infusion of OXT during training, rather than pretreatment before testing, had no effect on meth place preference (Qi et al., 2009).

Administration of OXT also has been shown to reduce alcohol preference and intake in a variety of voluntary drinking models in rats (Bowen et al., 2011, McGregor and Bowen, 2012) and mice (King et al., 2017, Peters et al., 2013). Specifically, pretreatment with OXT decreased binge-like alcohol consumption in a dose-related fashion, as well as reduced level responding and alcohol intake at doses that did not alter self-administration of a natural reward (sucrose) in mice (Koob, 2003). McGregor and Bowen (2012) found that a single dose of systemically administered OXT (1 mg/kg) produced a long-lasting reduction in preference for an alcohol-containing solution compared with a nonalcoholic sweet solution. Additionally, treatment with OXT for 2 weeks prior to the induction of a two-bottle free-choice drinking paradigm resulted in lower alcohol preference in OXT-treated rats compared to controls. MacFadyen et al. (2016) reported that systemic administration of a lower dose range of OXT (0.1–0.5 mg/kg) reduced operant alcohol self-administration in rats. Peripheral OXT treatment in a higher dose range (1–10 mg/kg) reduced alcohol consumption in male and female prairie voles that had two-bottle choice free-access to 15% alcohol (Stevenson et al., 2017a). In a continuous access paradigm, systemic OXT administration decreased alcohol intake in the first hour after treatment but had no significant effect on consumption over a 24-hour period (Stevenson et al., 2017a). Most recently, Tunstall et al. (2019) demonstrated that both systemic (intraperitoneal; ip.) and central (intracerebroventricular; icv.) OXT administration blocked escalated alcohol drinking and the enhanced motivation for alcohol in alcohol-dependent rats without altering these

behaviors in nondependent rats. This effect was also replicated with intranasal administration of OXT (Tunstall et al., 2019).

5. Role of Oxytocin in Alcohol/Drug Tolerance, Sensitization, and Withdrawal

Upon repeated use of a substance, the user develops neuroadaptive tolerance to the rewarding effects and an escalation of the dose is necessary to achieve the same initial pleasurable effects (Koob and Le Moal, 2001). As an individual continues further into the addiction cycle, neurochemical systems other than those involved in the positive rewarding effects of alcohol and drugs of abuse are recruited by chronic activation of the reward systems (Koob, 2013a, Koob, 2013b, Koob, 2013c, Koob and Le Moal, 2005). During this period, positive reinforcement associated with acute drug administration is gradually replaced by negative reinforcement, in which the drug is taken to prevent the emergence of negative emotional state (e.g. anxiety, irritability, dysphoria) when access to the drug is prevented. The switch to behavior driven by negative reinforcement is primarily mediated by brain stress systems (corticotrophin-release factor; CRF) in the HPA-axis and extended amygdala (Koob, 2008). Both stress- and drug-induced activation of the HPA-axis allows glucocorticoids to sensitize reward pathways, characterized by increases in reward thresholds during withdrawal (Koob and Kreek, 2007). As dependence and withdrawal develop, brain “anti-reward” systems, such a CRF, are recruited in the extended amygdala (Koob, 2013a) contributing to dysphoria and distress. Thus, the motivation to take drugs is not only driven by conditioned response cues, but by negative emotional states.

Oxytocin has been shown to modulate the development of acute and chronic tolerance to multiple drugs of abuse, including the analgesic effect of morphine and heroin (Kovacs et al., 1984, Kovacs et al., 1987), physiological effects of alcohol (i.e., sedative, ataxia, and hypothermic effects) (Szabo et al., 1987, Szabo et al., 1985, Szabo et al., 1989, Jodogne et al., 1991, Puciklowski et al., 1985, Tirelli et al., 1992), and sensitization to hyperactivity and stereotyped behavior associated with psychostimulants (Sarnyai et al., 1992). Early preclinical work demonstrated that both peripheral and central OXT dose-dependently attenuated the development of analgesic opioid tolerance and a single OXT injection (1 mg/kg) blocked the expression of established chronic opiate tolerance (Kovacs et al., 1985, Kovacs et al., 1984, Kovacs et al., 1987). Additionally, OXT pre-treatment inhibited the development of tolerance to morphine-induced hyper-locomotion (Kovacs et al., 1987) and anti-nociceptive effects (Kovacs et al., 1985) in mice. With regards to psychostimulants, higher doses of OXT have been shown to reduce locomotor hyperactivity and stereotyped behaviors induced by cocaine (Kovacs et al., 1990, Sarnyai et al., 1991, Sarnyai et al., 1992) and methamphetamine (Carson et al., 2010a, Qi et al., 2008), but not amphetamine (Sarnyai and Kovacs, 1994, Kovacs et al., 1985). Interestingly, lower doses of OXT were unable to prevent the development of tolerance or sensitization in rodents (Sarnyai et al., 1992). Repeated systemic administration (ip.) of OXT prevented the development of tolerance to the hypothermic, hypnotic and ataxic effects of alcohol (Jodogne et al., 1991, Szabo et al., 1985, Szabo et al., 1989). However, once tolerance had developed, OXT treatment had no effect on tolerance to the effects of alcohol (Szabo et al., 1985).

Evidence for a role for OXT in the regulation of withdrawal symptoms came from early seminal studies demonstrating that OXT administration decreased naloxone-precipitated morphine withdrawal symptoms in rats (Bicknell et al., 1988, Kovács and Van Ree, 1985). Oxytocin administration prior to alcohol exposure was also found to modulate the severity of alcohol withdrawal symptoms (e.g. picrotoxin-induced seizures) though these effects appear to be dose-dependent (Szabo et al., 1987). Additionally, central administration of OXT (icv.) was shown to block rapid tolerance to the effects of alcohol (Szabo et al., 1989). Interestingly, central administration was found to be more efficacious than peripheral administration, pointing to a centrally mediated mechanism (Szabo et al., 1989). Recent work by Manbeck and colleagues showed that OXT (0.06 −1.0mg/kg; i.p.) blocked withdrawal-induced elevations in somatic measures in nicotine-dependent rats (Manbeck et al., 2014). Further, Zanos et al. (2014) demonstrated that a single dose (6.4 mg/kg, ip.) of the OXT analogue carbetocin administered to morphine-dependent mice during withdrawal reduced levels of withdrawal-induced anxiety, depression and social anxiety behavior, suggesting a role for OXT in augmentation of withdrawal-related emotional dysregulation.

6. Oxytocin and Alcohol/Drug Relapse

Addiction is defined as a chronic relapsing disorder, in which individuals often return to compulsive drug taking after a period of abstinence (Koob and Volkow, 2010, Koob and Volkow, 2016). In an addicted individual, intense preoccupation with obtaining the abused substance develops and often precedes the somatic signs of withdrawal. This behavior, commonly described as craving, represents a shift from goal-directed behavior to habit driven (compulsive) behavior that results from drug-conditioned reinforcement, altered incentive motivation and maladaptive stimulus-response learning (Koob and Volkow, 2010). In other words, continued heavy use becomes a conditioned response to relieve and avoid withdrawal symptoms (e.g., withdrawal-induced seizures in alcoholics (Tabakoff and Hoffman, 2013).This stage of addiction primarily involves loss of prefrontal cortical executive control over intake (Everitt and Robbins, 2013). Hypofunction of cortical circuits are thought to play a permissive role in which subcortical structures that drive addiction are no longer inhibited (Koob, 2013c). As a result, circuits of the extended amygdala that mediate enhanced reactivity to stressful stimuli, dysphoria, anhedonia and increased craving drive behavior, ultimately leading to drug consumption (relapse).

A growing body of preclinical evidence suggests that OXT administration is effective in attenuating reinstatement of alcohol/drug seeking to conditioned cues, a drug prime, or stress. For example, systemic injection of OXT has been shown to reduce drug-primed reinstatement in models investigating heroin (Georgiou et al., 2015), cocaine (Zhou et al., 2014), and methamphetamine (Baracz et al., 2012, Carson et al., 2010a, Cox et al., 2017, Cox et al., 2013) relapse-related behaviors. In regard to cued reinstatement, systemic OXT decreased reinvigoration of drug-seeking behavior (lever responding) for cocaine (Bentzley et al., 2014, Leong et al., 2017) and methamphetamine (Bernheim et al., 2017) provoked by stimuli previously associated with drug reward. Similar results were found when OXT was administered centrally. More specifically, icv. infusion of OXT reduced cue-induced reinstatement of cocaine-seeking behavior in both male (Morales-Rivera et al., 2014) and female rats (Leong et al., 2016). Likewise, direct infusion of OXT into NAc (Weber et al.,

2018) and the subthalamic nucleus (STN), a downstream projection of the NAc (Leong et al., 2017), attenuated cocaine-seeking behavior. Both peripheral and central (icv) administration of OXT was effective in reducing cue- and drug-primed cocaine-or methamphetamine-seeking in both male and female rats, and the attenuation of this behavior was not dependent on cycle (Bentzley et al., 2014, Carson et al., 2010a, Cox et al., 2017, Cox et al., 2013, Leong et al., 2017, Leong et al., 2016, Weber et al., 2018, Zhou et al., 2014). Interestingly, repeated daily OXT (1mg/kg) treatment during adolescence attenuated methamphetamine-primed reinstatement during adulthood in female rats (Hicks et al., 2016). Similarly, repeated dosing of OXT (15 days; 1mg/kg, ip.) during a 30-day abstinence period from methamphetamine self-administration attenuated methamphetamine-primed reinstatement in both male and female rats (Everett et al., 2019). Though very few published studies have investigated the effects of OXT administration on reinstatement of alcohol-seeking behavior, central administration (icv.) of OXT was shown to reduced cue-induced alcohol relapse-like behavior in alcohol-dependent rats, but not in non-dependent rats (Hansson et al., 2018).

Oxytocin has also been shown to be effective in reducing stress-related relapse-like behavior. Systemic administration of OXT decreased methamphetamine-seeking behavior following predator odor exposure (Ferland et al., 2016) and yohimbine administration (Cox et al., 2013) in rats. Additionally, repeated dosing of OXT during a forced abstinence period attenuated yohimbine-induced reinstatement of methamphetamine-seeking behavior (Everett et al., 2019). In mice, centrally administered OXT (icv.) attenuated reinstatement of methamphetamine CPP induced by restraint stress (Qi et al., 2009, Han et al., 2014), and systemic administration of the OXT analog, carbetocin, reduced the effects of forced-swim stress on reinstatement of morphine-induced CPP (Zanos et al., 2014). Finally, peripherally administered OXT across a range of doses (0.1–1mg/kg; ip.) attenuated alcohol-seeking behavior induced by yohimbine administration or exposure to predator odor in male and female mice (King and Becker, 2019).

7. Neurobiological Interactions

Dopamine-

The mesolimbic dopamine pathway, connecting the VTA to the NAc, plays a key role in the rewarding properties of almost all drugs of abuse. Oxytocin appears to modulate reward signaling in the mesolimbic dopamine system through direct interaction with multiple neurotransmitter systems. Oxytocin projections from the PVN synapse on dopaminergic terminals within the NAc (Knobloch and Grinevich, 2014) and OXTRs are present on VTA dopaminergic projection neurons that target the NAc and medial PFC (Knobloch and Grinevich, 2014, Peris et al., 2017). Central OXT administration has been shown to inhibit drug and alcohol induced increases in dopamine in mesolimbic regions, particularly the NAc (Kovacs et al., 1998, Peters et al., 2017). For instance, intra-NAc infusion of OXT blocked cocaine-induced increases in dopamine utilization (Kovacs et al., 1998) and intracerebroventricular infusions of OXT inhibited methamphetamine-induced dopamine turnover in the NAc (Qi et al., 2008). Similarly, systemically administered OXT decreased methamphetamine-induced activation of the NAc and STN (Carson et al., 2010b). In support

of these findings, direct infusion of OXT into the NAc or STN attenuated the development of methamphetamine-induced conditioned place preference (CPP) (Baracz et al., 2012). Viral-mediated overexpression of OXTRs in the NAc reduced alcohol-induced CPP and alcohol consumption in mice (Bahi, 2015, Bahi et al., 2016). Moreover, alcohol-induced elevation of dopamine release within the NAc was blocked by OXT administration (icv.), and this inhibition was associated with a reduction in alcohol preference and consumption in rats (Peters et al., 2017). Additionally, recent studies have characterized the presence of OXT/dopamine heteroreceptor complexes (OXTR/D2R) within the NAc and central amygdala, where OXTR activation was shown to increase D2 receptor signaling (de la Mora et al., 2016, Fuxe et al., 2012, Romero-Fernandez et al., 2013). Interestingly, the D2 receptor subtype is downregulated following chronic drug exposure and activation of DR2 has been shown to reduce drug-seeking behavior (Volkow and Morales, 2015). Thus, OXT, serving as an allosteric agonist to increase D2R affinity in the NAc, may reduce drug-seeking behavior.

HPA AXIS-

Oxytocin has been reported to reduce activity of the HPA-axis under basal conditions as well as following exposure to various stress events/stimuli (Jurek et al., 2015, Neumann et al., 2000b, Peters et al., 2014, Slattery and Neumann, 2010, Knobloch et al., 2012). Oxytocin dampens stress-induced HPA-axis activation (as indexed by elevated circulating corticosteroid levels), as well as reduces stress-related behavioral responses in animal models of anxiety and depression (Neumann et al., 2000a, Windle et al., 2004). More specifically, central OXT administration (icv.) decreased stress-induced corticosterone release in rats (Windle et al., 1997), whereas intra-PVN administration of OXTR antagonist reduced ACTH release in response to force swim stress (Neumann et al., 2000b). Further, at baseline high levels of OXT and OXTR mRNA expression are localized in forebrain regions such as the extended amygdala, where OXT signaling can play a significant role in the regulation of anxiety, stress, and reward-related behaviors (Dabrowska et al., 2011, Gimpl and Fahrenholz, 2001, Veinante and Freund-Mercier, 1997, Martinon and Dabrowska, 2018). Oxytocin was also found to directly attenuate stress-induced synthesis of CRF within PVN via specific intracellular signaling pathways (Knobloch et al., 2012). These OXT-CRF interactions, especially within the PVN and extended amygdala, are likely play a critical role stress reactivity related to relapse.

Vasopressin-

A large body of evidence exists to support “cross-talk” among the related peptides OXT and vasopressin (AVP) and their receptors, though the mechanisms and functional significance of such OXT-AVP interactions remain poorly understood (Chini et al., 2017; see review: Carter et al., 2017). The two hypophyseal neuropeptide systems generally produce opposing physiological actions; central oxytocin dampens HPA-axis activity and exerts anxiolytic effects whereas AVP enhances CRF-activation of the HPA-axis, increasing anxiety and depressive-related behaviors (Neumann and Landgraf, 2012). Due to high structural homology, OXT also binds to and activates AVP receptor subtypes (V1a, V1b and V2) (Knobloch and Grinevich, 2014). Under some conditions, this may constitute alternative targets for OXT, especially at high local concentrations and in brain regions that have little or no OXTR expression (Grinevich et al., 2016, Manning et al., 2008). Further, adding to the

complexity of OXT and AVP interactions is the possibility that OXT and AVP receptors can form heterodimers with unknown results on peptide binding (Chini et al., 2017). Interestingly, a role for AVP has been implicated in the transition to alcohol dependence (Zhou and Kreek, 2018) and AVP receptor antagonism (V1b) has been shown to decrease alcohol intake in rodents (Zhou and Kreek, 2018, Edwards et al., 2012, Katz et al., 2016) as well as reduce nicotine and alcohol consumption in humans (Ryan et al., 2017). It is noteworthy, however, that while activation of OXTR reduces alcohol consumption (Passoni et al., 2016, Bahi, 2015), antagonists of the V1b receptor also reduce alcohol drinking (Zhou and Kreek, 2018, Edwards et al., 2012, Katz et al., 2016), suggesting that it is unlikely that OXT produces this effect via activation of AVP (V1b) receptors. Nevertheless, the potential for OXT and AVP systems to operate cooperatively in regulating alcohol/drug taking behavior is a possibility that requires more experimental attention.

GABA-

Oxytocin also appears to directly interact with the GABAergic system, which may be of particular significance for alcohol addiction. Oxytocin receptors have been localized on GABAergic interneurons in the NAc (Dolen et al., 2013), central amygdala (Huber et al., 2005), hippocampus (Zaninetti and Raggenbass, 2000) and PFC (Li et al., 2016, Nakajima et al., 2014). There is also some evidence that OXTR-expressing cells contain GABA (Yoshida et al., 2009), implicating a role for OXT in the modulation of inhibitory tone. Indeed, OXT administration has been shown to effect GABAergic transmission in multiple brain regions critical to the addiction process and may regulate both drug-seeking and anxiety-related behaviors through interactions with its own receptor or by binding directly to GABA receptors (Bowen et al., 2015). For instance, OXT administration blocked the faciliatory effects of acute alcohol on GABA in the central amygdala of alcohol dependent, but not nondependent rats (Tunstall et al., 2019). Additionally, there is some evidence to suggest that OXT may also modulate GABAergic transmission via direct interaction with $GABA_A$ receptors (Bowen et al., 2015, Dong et al., 2017). More specifically, OXT has been shown to act directly on extra synaptic delta subunit-containing $GABA_A$ receptors to block the positive allosteric modulation of these receptors by alcohol (Bowen et al., 2015).

Glutamate-

There is some evidence to suggest OXT interreacts with the glutamatergic system, through OXTRs located on astrocytes (Dolen et al., 2013) within the NAc to modulate drug-seeking behavior. In support of these mechanism, mGlur2/3 receptor antagonism reversed the attenuating effect of OXT on cocaine and methamphetamine-seeking behavior (Bernheim et al., 2017, Weber et al., 2018). Further, Qi and colleagues demonstrated that pretreatment with OXT reduced stress-induced, but not methamphetamine-primed, increases in glutamate levels in mPFC of mice during methamphetamine place-preference reinstatement testing (Qi et al., 2009).

Noradrenaline-

There is also some preliminary evidence for an interaction between the oxytocinergic and noradrenergic system. In support of this mechanism, pretreatment with OXT attenuated reinstatement of alcohol-seeking in mice (King and Becker, 2019) and methamphetamine-

seeking in rats (Cox et al., 2013, Everitt and Robbins, 2013) induced by yohimbine, an alpa-2 receptor antagonist. Further, the ability of OXT to attenuate morphine-primed reinstatement of CPP in mice has been associated with the ability of OXT to suppress striatal noradrenaline turnover (Georgiou et al., 2015). Oxytocin administration has been shown to enhance noradrenaline release in the SON, whereas stressful stimuli and food intake activate hypothalamic OXT neurons, at least in part, by noradrenergic neurons in the nucleus tractus solitarius (Onaka et al., 2012). Oxytocin receptors may also interact with a2 adrenergic receptors (a(2A)ARs) in a similar fashion (Fuxe et al., 2012) to dopamine receptors. More specifically, OXT via signaling at OXTR-a(2A)AR heteroreceptor complex may act as an allosteric antagonist to reduce adrenergic signal transduction (Diaz-Cabiale et al., 2000). It is also likely that a(2A)ARs can also modulate OXTRs through reciprocal receptor-receptor interaction (Fuxe et al., 2012). Interestingly, OXTR-(2A)AR heterodimers have been located within hypothalamic and amygdala regions as well as the nucleus of the solitary tract (NTS), which is well situated to mediate both central and autonomic stress effects (Diaz-Cabiale et al., 2000, Fuxe et al., 2012) that may be involved in withdrawal-related symptoms and stress-related relapse.

8. Clinical trials with Oxytocin

Clinically, OXT administration has shown some efficacy in attenuating craving and withdrawal-related symptoms across alcohol and multiple drugs of abuse. In the context of stress, a single dose of IN OXT was shown to reduce stress-induced craving and anxiety in cannabis-dependent individuals (McRae-Clark et al., 2013). However, Reed and colleagues demonstrated that IN OXT produced an increase in subjective stress compared to placebo in female cannabis users, whereas IN OXT produced a small (but non-significant) decrease in subjective stress in males (Reed et al., 2019). The authors found no differences in stress-related cannabis craving, though female cannabis users demonstrated a longer latency to self-administer and used less cannabis overall compared to males (Reed et al., 2019). In a study by Lee et al. (2014) a single dose of IN OXT reduced the desire to use drug in cocaine-dependent subjects, though OXT treatment had no effect on cue-induced cocaine craving (Lee et al., 2014). In contrast, Hansson et al., (2018) showed that intranasal OXT reduced cue reactivity in male heavy drinkers in the insula, prefrontal and limbic regions. These results were supported by a recent study by Joseph et al., (2019) which demonstrated reduced cue reactivity in male and female cocaine users in dorsal medial PFC. Interestingly, male cocaine users with a history of childhood trauma also showed reduced cue reactivity in the amygdala on OXT, though this effect was not present in females (Joseph et al., 2019). In heroin-dependent men, intranasal administration of OXT reduced craving and withdrawal scores but did not significantly impact measures of anxiety (Moeini et al., 2019). The single dose of IN OXT also had a positive effect on stress-related hormone levels, reducing serum cortisol level and cortisol/dehydroepiandrosterone sulphate (DHEAS) ratio following cue-induced craving task during abstinence compared to control patients (Moeini et al., 2019). Similarly, in patients with a dual diagnosis of PTSD and AUD, IN OXT attenuated cortisol reactivity in response to a stress provocation (Flanagan et al., 2018). Further, IN OXT treatment decreased alcohol withdrawal symptoms in treatment-seeking patients compared to placebo and significantly reduced anxiety in dependent subjects following cessation of

drinking (Pedersen, 2017, Pedersen et al., 2013). Taken together, OXT treatment may be a useful therapeutic to reduce stress-related physiological responses (e.g. anxiety, craving) relevant to drug and alcohol use and relapse, though future studies are necessary in alcohol and drug dependent populations.

9. Brain Penetrance and Pharmacological Tools

The potential therapeutic utility of OXT will invariably depend on its effectiveness following its systemic administration. This raises the question as to whether peripheral administration of the neuropeptide effectively penetrates the blood-brain barrier to influence brain function (Lee et al., 2018). Historically, peripherally administered OXT was not thought to pass through the blood-brain barrier in quantities sufficient to alter behavior (Opacka-Juffry and Mohiyeddini, 2012) but rather, impact behavior via a feed-forward mechanism that involves stimulated release of endogenous OXT (Rossoni et al., 2008, Ludwig et al., 2002, Ermisch et al., 1985). However, a number of studies have recapitulated effects of systemic OXT administration with direct (icv. or site-specific) intracranial infusions across a number of behavioral tasks (Cox et al., 2017, Lee et al., 2018, Slattery and Neumann, 2010, Windle et al., 1997, Love, 2014, Ring et al., 2006). Additionally, peripheral administration of OXT has been shown to induce Fos expression in OXT neurons in the PVN (Carson et al., 2010b, Leong et al., 2017), suggesting that peripheral administration may induce endogenous central release. In a recent study, Smith et al., (2019) reported detectable concentrations of OXT in amygdala and hippocampus of OXT null mice following both intranasal and intraperitoneal administration of the neuropeptide. These data validate that the source of measured OXT originates solely from exogenous administration, as the genetically deficient (knockout) mice do not produce endogenous OXT. However, Lee et al. (2018) demonstrated that while OXT administered through intranasal and intravenous routes of administration increased OXT levels in cerebral spinal fluid, it did not activate a feed forward mechanism to elevate endogenous OXT. Thus, while studies are largely consistent regarding elevated OXT in the CNS following peripheral administration, the mechanism by which exogenous OXT delivered in the periphery activates OXT signaling in the brain remains unclear. Further studies are needed to address this issue, as it is relevant to the potential for OXT to serve as a therapeutic for alcohol/drug addiction.

There is considerable interest in using OXT-like molecules and OXTR modulators as therapeutics. A number of non-peptide OXTR agonists are in development or in clinical trials and offer potential benefits in both research and therapeutic settings (Frantz et al., 2018, Manning et al., 2008, Wiśniewski, 2019). The oxytocin analogue carbetocin is currently the most widely used OXTR agonist drug in the clinical setting. Carbetocin is utilized to control postpartum hemorrhage and it is noted for its extended half-life as compared to OXT (Jin et al., 2019). In preclinical addiction research, carbetocin has been shown to effectively attenuate the reinstatement of drug seeking (Georgiou et al., 2015, Zanos et al., 2014). Carbetocin also has been shown to reduce alcohol reward (Bahi, 2015, Rae et al., 2018). Other signaling molecules may act as modulators of OXTR and can potentially be utilized to therapeutic advantage. For example, it has been shown that cholesterol and divalent cations such as Mn^{2+} and Mg^{2+} are positive allosteric modulators (PAM) of the OXTR that act by stabilizing the receptor in a high-affinity state (reviewed in

Gimpl et al., 2002, Gimpl et al., 2008). The discovery and development of new drugs that selectively target the OXTR will be key for future studies on the clinical utility of this therapeutic strategy for alcohol/drug addiction treatment.

10. Conclusions

In light of the preclinical and clinical literature reviewed here, OXT plays a key role in mediating several addiction-related behavioral and neurochemical processes and should be considered a promising target for the treatment of alcohol and substance use disorders. Oxytocin is intricately intertwined with neurotransmitter (e.g. dopamine, GABA, glutamate) and other central and peripheral signaling systems (e.g. noradrenaline, CRF, corticosterone) involved in the development and maintenance of addiction. Oxytocin signaling has been shown to interact with various drugs, and alcohol in particular, across the cycle of use disorders: it is part of the brain signaling cascade that creates and modulates reward and pleasure in response to drugs, as well as being able to alter the course of drug withdrawal. Additionally, OXT interacts with brain stress systems to modulation common triggers for relapse such as emotionality, anxiety and stress reactivity. However, due to its diverse interactions with neurobiological systems and its wide range of roles in governing behavior, OXT is also sensitively subject to the effects of characteristics such as species, sex, and the dose at which it enacts its various effects. Thus, understanding the nuances of OXT signaling is germane to unlocking its potential as a therapeutic target for the treatment of alcohol and substance use disorders.

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Highlights

- Oxytocin signaling is altered by chronic alcohol or drug exposure
- Peripheral and central OXT administration influences the development of tolerance, sensitization and withdrawal symptoms, and modulates motivation to seek and consume alcohol and drugs in preclinical models
- Oxytocin interacts with the hypothalamic-pituitary-adrenal axis and multiple neurotransmitter systems within addiction circuitry
- Intranasal OXT reduces withdrawal symptoms, craving and cue-reactivity in cannabis-, cocaine-, alcohol- and heroin- dependent populations