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Oxytocin for the treatment of drug and alcohol use disorders

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Abstract

There is growing interest in the use of oxytocin (OT) as a potential treatment for alcohol and other substance use disorders. OT is a neuropeptide that modulates adaptive processes associated with addiction including reward, tolerance, associative learning, memory, and stress responses. OT exerts its effects via interactions with the hypothalamic–pituitary–adrenal (HPA) axis, and multiple neurotransmitter systems including the dopamine mesolimbic reward and corticotrophin-releasing factor stress systems. Oxytocin effects on stress systems are of high interest given the strong link between stress, drug use and relapse, and known dysregulation of HPA-axis activity associated with substance use disorders. At the same time, the oxytocin system is itself altered by acute or chronic drug exposure. This review summarizes the preclinical and clinical literature on the oxytocin system, and its relevance to drug and alcohol addiction. In addition, findings from recent clinical trials conducted in participants with cocaine, cannabis or alcohol use disorder are included and evidence that oxytocin may help to normalize blunted stress responses, and attenuate withdrawal associated hypercortisolism, negative mood and withdrawal symptoms are summarized.

Keywords

Oxytocin; addiction; dependence; substance use disorder; alcoholism; treatment

Introduction

Oxytocin (OT) is a 9 amino acid polypeptide hormone that acts via a specific receptor and is widely distributed in the central nervous system (CNS) and peripheral tissues (Gimpl and Fahrenholz 2001). OT is involved in the regulation and release of adenohypophyseal hormones including prolactin, adrenocorticotropin (ACTH), gonadotropins, and corticotrophin-releasing factor (CRF). Initially, OT was thought to be primarily involved in sexual behaviors, female parturition and lactation. Subsequent research has determined that OT is also involved in emotional regulation, pain and stress, and modulates response to rewarding behaviors promoted by food, sex and drugs (Meyer-Lindenberg et al. 2011;

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Onaka et al. 2012). The co-modulation of both stress and motivational processes is believed to be due to the important role of OT to shift salience to social, affiliative processes, both by increasing the salience itself of rewarding stimuli and/or by reducing stress, allowing for attention to social bonding (Baskerville and Douglas 2010). This is obviously relevant to addiction, where salience of drug stimuli overshadows motivation for social affiliation, and where stress may trigger drug seeking and relapse (Sinha 2008). In the current review, we will focus on the role of the oxytocin system in drug and alcohol addiction and highlight key findings to date on the use of intranasal OT to treat substance use disorders.

Oxytocin and stress

The influence of OT to dampen stress responses is important. Neuroendocrine pathways that modulate the response to stress include three interconnecting circuits, the HPA axis, the adrenomedullary system, and the extra-hypothalamic CRF system. The HPA axis releases CRF from paraventricular neurons within the hypothalamus, stimulating the synthesis and release of adrenocorticotropin (ACTH) by the anterior pituitary, which in turn stimulates the synthesis and release of corticosteroids (CORT) (cortisol in human and nonhuman primates and corticosterone in rodents) via the adrenal cortex. The sympathetic adrenomedullary system, which releases norepinephrine and epinephrine, and CRF expression in the extra-hypothalamic brain regions including limbic regions, are key substrates involved in anxiety and other stress-related behaviors. Stress, defined as any stimulus that disrupts physiological homeostasis, triggers a cascade of adaptive responses involving any or all of these pathways to return the organism to homeostasis.

There is strong evidence from the preclinical literature that stress exposure is an important contributor to relapse. In rats and monkeys, acute stress enhances alcohol preference and reward (Funk et al. 2004), and increased alcohol intake is correlated with stress-induced increases in CORT levels (Fahlke et al. 2000; Fish et al. 2008). In addition, following repeated social stress exposure (e.g., defeat, low social rank, and maternal separation), rats and monkeys subsequently show greater alcohol intake when compared to non-stressed cohorts (Fahlke et al. 2000; Cruz et al. 2008; Fish et al. 2008). Current theories suggest that CORT release induced by stress augments drug reinforcement. Indeed, in rodents, CORT increases drug reward by increasing mesolimbic dopamine transmission (Piazza and Le Moal 1996), rats self-administer CORT itself at levels similar to those elicited by stress, and intracerebroventricular infusions of CORT enhance the reinforcing effects of alcohol (Fahlke et al. 1996).

Studies in laboratory animals have demonstrated that OT has marked anti-stress effects. When administered centrally, OT decreases stress-induced increases in CORT levels (Lang et al. 1983; Windle et al. 1997; Neumann et al. 2000) and reduces stress-induced behaviors in rodent models of anxiety and depression (Arletti and Bertolini 1987; Insel and Winslow 1991; Windle, et al. 1997; Neumann et al. 2000). At the same time, the endogenous OT system appears to be sensitive to stressors. In rats, exposure to acute stress increased OT levels in blood and in hypothalamic and extra-hypothalamic brain regions (Lang et al. 1983; Neumann et al. 1998; Ebner et al. 2000; Ondrejcakova et al. 2010) and increased OT mRNA levels (Jezova et al. 1995). Thus, OT appears to play a protective role in homeostatic

regulation of stress responses, and OT administration may attenuate the effects of stress on drinking/drug use and relapse (Uhart and Wand 2009; Koob et al. 2014).

Investigations in human subjects are in line with the preclinical literature. When administered via the intranasal route, OT produces changes in measures of autonomic arousal and mood (MacDonald et al. 2011), increased positive communication during couples' conflict discussions (Ditzen et al. 2009) and improved recognition and processing of positive facial expressions (Di Simplicio et al. 2009; Marsh et al. 2010; Lischke et al. 2012). The anti-stress effects of OT have been also been investigated using the Trier Social Stress Test, a well-validated laboratory procedure for induction of stress responses in human subjects (Foley and Kirschbaum 2010). This test, which includes components of public speaking component and oral mental arithmetic, produces a robust increase in CORT and self-reported psychological stress and these effects are attenuated by OT (Heinrichs et al. 2003; Quirin et al. 2011; Simeon et al. 2011; de Oliveira et al. 2012; Kubzansky et al. 2012). Consistent with an OT anti-stress hypothesis, a recent study that measured both OT and CORT after the TSST found that salivary OT levels increased immediately following social stress exposure, prior to increases in salivary CORT (Jong et al. 2015). Taken together, these data suggest that OT treatment may be useful to normalize the HPA-axis and reduce stress-related physiological and subjective responses (e.g., anxiety, craving) that increase drug and alcohol use and trigger relapse.

The endogenous OT system and chronic drug use

OT, the related peptide, vasopressin, and their respective receptors are highly conserved in evolution (Beets et al. 2012). The OT receptor belongs to the rhodopsin-type (class1) G protein-coupled receptor family and was cloned in 1992 (Kimura et al. 1992). Studies in laboratory animals have demonstrated that OT is synthesized in the magnocellular neurons of the paraventricular (PVN), supraoptic (SON) and accessory magnocellular (AN) nuclei of the hypothalamus and released into the bloodstream from axon terminals of these neurons, which are located in the posterior pituitary. Central release of OT occurs by two mechanisms (Ross and Young 2009). 1) There is dendritic release from the PVN and SON in the hypothalamus (Ludwig and Leng 2006) with passive diffusion to OT receptors, which are located throughout the brain (Gimpl and Fahrenholz 2001). 2) More targeted direct release of OT occurs from nerve terminals of parvocellular neurons of the PVN, which project centrally to diverse regions including, among others, the olfactory bulb, tubercule, medial and central amygdala, lateral septum, hippocampus(HC), brainstem and spinal cord (Stoop 2014).

There is evidence that chronic exposure to drugs of abuse produces compensatory neuroadaptive changes in the endogenous OT system in specific brain regions involved in addiction processes. The direction of change is region-specific. For example, OT receptor density in the rodent amygdala and hypothalamus increases following chronic administration of methamphetamine, cocaine and morphine (Zanos et al. 2014a,b, Georgiou et al. 2015), while in the hippocampus (HPC), decreased levels of OT and/or OT receptor density were reported following chronic administration of cocaine (Sarnyai and Kovacs 1994) or morphine (Zanos et al. 2014a). Chronic self-administration of methamphetamine also results

in decreased OT receptor immunoreactive fibers in the nucleus accumbers (NAc) Core compared to yoked controls (Baracz et al. 2015b). Chronic exposure to Δ^9 – tetrahydrocannabinol in rats downregulates OT mRNA expression in the NAc and ventral tegmental area (VTA) (Butovsky et al. 2006). Chronic administration of morphine to rats alters brain OT expression differentially with a decrease in OT mRNA in the SON and NAc and an increase in the VTA and locus coeruleus (You, Li et al. 2000).

To date, studies in humans are limited to post-mortem autoradiography studies and examination of circulating OT. In alcoholic individuals, plasma OT levels were decreased (Marchesi et al. 1997) and OT immunoreactivity was decreased in the hypothalamus post-mortem (Sivukhina et al. 2006). A final common pathway of drugs and alcohol is activation of stress as well as reward processing (Koob et al. 2014). It is unknown how activation of either of these pathways results in a decrease of OT synthesis, especially when in general stressors are associated with an activation of OT systems (Light et al. 2004; Hoge et al. 2008; Taylor, et al. 2010; Jong et al. 2015). Apart from the effect of the drugs of abuse on the endogenous OT system, environmental factors such as stress and traumatic social experiences all contribute to the emergence of individual differences in the endogenous OT system that may then contribute to the development of addiction (Buisman-Pijlman et al. 2014). Overall, it is also unknown if administration of exogenous OT will reverse these changes in OT synthesis created by exposure to drugs of abuse and whether this would translate to reversal of addictive behaviors. or if administration of OT can prevent the development of addiction after exposure to environmental risk factors. Lastly, the relationship between peripheral OT levels in plasma and central levels of OT is not known, but they are thought to be separately regulated (Ludwig and Leng 2006); therefore, studies that use plasma OT as a surrogate for central OT function are of limited value.

Preclinical studies examining the effect of oxytocin on drug-seeking behavior

Interest in OT as a modulator of the neurobehavioral response to alcohol and other drugs of abuse stems from work done in the 1970’s by De Wied and colleagues (Bohus et al. 1978), who demonstrated that hypophyseal hormones modulate learning and memory, with OT generally having an inhibitory effect. Since current theories conceptualize addiction as a form of maladaptive learning, a large number of preclinical studies in rodents have investigated the effect of OT on various drug-related behaviors, to determine whether OT could reverse the neuroadaptations occurring with repeated drug and alcohol use (Sarnyai and Kovacs 1994).

Since the majority of the published literature has focused on the effects of OT on behavioral and neurochemical responses to opiates, psychostimulants and alcohol we summarize those studies below.

Opiates

Early preclinical studies focused on the effect of OT to modulate the development of acute and chronic tolerance to the analgesic effect of morphine and heroin is reduced with a single

dose of OT, while higher doses of OT are required to reduce established chronic tolerance (Kovacs et al. 1984, 1985b, 1987). Further, administration of an OT receptor antagonist inhibits this effect on tolerance, suggesting that the endogenous OT system opposes the development of acute tolerance (Kovacs et al. 1987). Moreover this effect appears to be centrally mediated as intracerebroventricular (ICV) injections of OT are more potent in their action to inhibit acute and chronic tolerance, as are localized injection into the HPC or NAc or administration of dipeptides derived from the C-terminal OT portion (Kovacs et al. 1985). OT also delays naloxone-induced withdrawal symptoms in a dose dependent manner (Kovacs et al. 1984, 1985b).

With respect to self-administration behavior, OT decreases both the acquisition and maintenance of heroin self-administration (Kovacs et al. 1985b). This effect is reproduced with injection of OT into the NAc or HPC (Ibragimov et al. 1987). However, the effect of OT on heroin self-administration was tested with only one dose of heroin (Kovacs et al. 1985a); therefore, without dose –response information, it is not possible to determine whether OT was inhibiting or potentiating the effects of heroin. OT given ICV increased the expression of morphine-induced conditioned place preference(Moaddab, Hyland et al. 2015). This effect may be explained in part by a well described effect of acute morphine to inhibit OT cell firing in the hypothalamus, with tolerance developing to this effect with repeated administration of morphine (Bicknell et al. 1988). During morphine withdrawal there is a rebound hyper-excitation of these cells with increased release of OT (Bicknell et al. 1988). |In light of this effect, administration of OT after conditioning with repeated injections of morphine may signal a withdrawal state, which then drives the increased conditioned place preference observed in this study (Moaddab et al. 2015). Further evidence that OT is involved in withdrawal from morphine, is that peripheral administration of carbetocin, an OT analogue, inhibits the development of anxiety and depressive behaviors and improves social behaviors during morphine withdrawal, as well as preventing stress-induced reinstatement of conditioned place preference for morphine (Zanos et al. 2014). . These results are consistent with those from Qi et al. (2009) who reported an inhibitory effect of OT on stress-primed reinstatement of conditioned place preference for methamphetamine.

In summary, there is evidence that OT inhibits tolerance to opiates, and reduces opiate self-administration, and stress-induced reinstatement of extinguished opiate-taking behaviors. At the same time, it is not clear if changes in OT levels during early drug withdrawal have a positive or negative impact on withdrawal severity and drug-taking behaviors. The increase in endogenous OT release during withdrawal may drive opiate-seeking behavior in the withdrawal state, but may also ameliorate behavioral disturbances that occur during opiate withdrawal.

Psychostimulants

Early preclinical work examined the effects of OT on psychostimulant-related behaviors. For example, OT reduced locomotor hyperactivity and stereotyped behaviors induced by cocaine (Kovacsi et al. 1990; Sarnyai et al. 1990, 1991), but not amphetamine (Kovacs et al. 1985b; Sarnyai and Kovacs 1994).

More recent preclinical work on psychostimulants has focused on methamphetamine, probing the mechanism underlying the largely inhibitory effect of OT on locomotor hyperactivity, self-administration and conditioned place preference (Qi et al. 2008, 2009; Carson et al. 2010a,b;Baracz et al. 2012; Baracz and Cornish 2013; Han et al. 2014; Bahi 2015). The recent studies examining the mechanism of drug-, stress- or cue-induced reinstatement of conditioned place preference or drug-seeking behavior on balance show that OT has an effect on all of these animal models, with some evidence that the mesocorticolimbic system is involved in modulating these effects. It should be noted, however, that there are inconsistent results with respect to the direct involvement of the OT receptor in the reported inhibitory effects; these studies are reviewed below.

One preclinical paradigm, conditioned place preference (or aversion) involves pairing repeated drug administration with a specific environment, and association of a different environment with the absence of the drug, to measure the rewarding effects of the test drug. , OT has been reported to reduce the acquisition, but not the expression, of methamphetamine-induced conditioned place preference (Qi et al. 2009). This suggests that OT reduces the rewarding effect of methamphetamine and perhaps does less to inhibit memory retrieval processes. The potential application of OT as a preventative treatment for the development of addictive behaviors was examined by Hicks and colleagues who treated female rats with daily systemic OT during adolescence and found a reduction in responding for methamphetamine under a progressive ratio schedule and reduced reinstatement to a methamphetamine prime, as well as higher plasma OT levels, compared to untreated rats (Hicks et al. 2016).

Reinstatement models of drug relapse include both operant self-administration models and place conditioning models. OT studies report mixed results depending on the reinstatement paradigm used (conditioned place preference vs. self-administration). OT decreases both stress- and cue-, (but not drug-) primed reinstatement of methamphetamine-conditioned place preference (Qi et al. 2009; Han et al. 2014; Morales-Rivera et al. 2014) . The effect of OT to reduce stress- (but not drug-) primed reinstatement of conditioned place preference for methamphetamine was accompanied by a reduction in medial prefrontal cortical (mPFC) glutamate levels as measured by microdialysis (Qi et al. 2009). This effect was reversed by an OT antagonist. The effect of OT on stress priming of the reinstatement of conditioned place preference was further explored by microinjecting OT into the dorsal HPC and mPFC (Han et al. 2014). Stress-induced reinstatement was inhibited by OT injected into the mPFC and reversed with an OT receptor antagonist. It was also inhibited when injected into the dorsal HPC, albeit at a higher dose and this effect was not reversed by an OT receptor antagonist.

Local administration of OT into the subthalamic nucleus or the NAc core decreased methamphetamine-induced reinstatement of self-administration (Baracz et al. 2015a, 2016). These effects were not reversed with co- administration of an OT antagonist suggesting that OT does not directly modulate methamphetamine relapse behavior, and that other receptor systems are likely involved.

Zhou and colleagues examined the effect of OT on cocaine self-administration under different reinforcement schedules and conditions of drug availability, as well as cue- and drug-primed reinstatement of cocaine- and sucrose-seeking behavior (Zhou et al. 2015). OT dose-dependently reduced cocaine self-administration under conditions of increasing motivational demands (i.e., progressive ratio schedules) and reduced the maximal amount of work (breakpoint) for a cocaine injection. OT also reduced the effects of cocaine- or cue-induced reinstatement of extinguished cocaine self-administration behavior (i.e., cocaine seeking) and reversed cocaine-induced changes in glutamate receptor function (Zhou et al. 2015)

Alcohol

Recent preclinical data show that administration of OT may disrupt biobehavioral adaptions associated with long-term alcohol exposure (Sarnyai and Kovacs 1994; McGregor and Bowen 2011). Early studies with OT focused on the ability of the peptide to reduce or reverse tolerance. A single dose of OT had no effect on tolerance; however, repeated dosing prior to alcohol decreased tolerance to the hypothermic response to alcohol (Szabo et al. 1985, 1989). Interestingly, once tolerance had developed, administration of OT had no modulatory effect on tolerance (Szabo et al. 1985). In alcohol-naïve or alcohol-dependent mice, a single dose of OT had no effect on the severity of picrotoxin-induced seizures (Szabo et al. 1987). In contrast, OT, administered before alcohol daily, resulted in a milder intensity of alcohol withdrawal seizures precipitated by picrotoxin (Szabo et al. 1987), suggesting rapid reversal of tolerance. In addition, OT reduces dthe evelopment of rapid tolerance to the hypnotic, myorelaxant effects of alcohol (Rigter et al. 1980; Pucilowski et al. 1985; Szabo et al. 1985, 1989), and produces a prolonged attenuation of alcohol withdrawal symptoms (Szabo et al. 1987; Kovacs et al. 1998; McGregor and Bowen 2011).

For self-administration, large doses of OT administered either peripherally or centrally have no effect on alcohol drinking using a two-bottle free-choice paradigm (Peters, Slattery et al. 2013). However, McGregor and Bowen (2012) found that a single dose of OT, 1 mg/kg, reduced preference for an alcoholic beverage as compared to a non-alcoholic sweet solution, and this effect lasted for up to six weeks. Further, OT treatment for 2 weeks before the introduction of a two-bottle choice paradigm also resulted in a significantly lower alcohol preference in OT-treated compared to control rats. MacFadyen and colleagues recently reported that OT at lower doses (0.1-0.5 mg/kg i.p.) administered systemically reduced alcohol self-administration (MacFadyen et al. 2016). In a chronic intermittent access model, OT administered ICV acutely similarly reduced ethanol self-administration and also blocked ethanol-induced dopamine release in the NAc, in both ethanol-naïve and chronically exposed rats (Peters et al. 2016), highlighting a possible mechanism for the behavioral effect observed.

Consistent with these results, administration of the OT receptor agonist carbetocin or genetic over-expression of OT receptors in the NAc via a lentiviral vector decreased acquisition and alcohol-primed reinstatement of conditioned place preference and increased rates of extinction (Bahi 2015). However, while the OT receptor seems to be involved in the rewarding properties of ethanol and this appears to involve the ventral striatum, the sedative

and ataxic effects of alcohol do not appear to be mediated by the OT receptor (Bowen et al. 2015).

Overall, there is evidence that OT, administered systemically or centrally, reduces self-administration of opiates, cocaine and alcohol and reinstatement of responding induced by exposure to drug cues and stress. The mechanisms seem to involve the midbrain dopaminergic as well as medial prefrontal glutamatergic pathways.

Human Studies of OT in Alcohol and Drug Dependence

There are relatively few human studies that have examined the effects of OT in subjects with alcohol and drug dependence. Heavy alcohol drinking is associated with dysregulation of HPA-axis activity, as shown by episodes of hypercortisolism between drinking bouts and a blunted CORT response to stress during early abstinence (Kemper et al. 1990; Wand and Dobs 1991; Errico et al. 1993; Vescovi et al. 1997; Boschloo et al. 2011). A blunted CORT response has been associated with increased anxiety and craving during acute abstinence and subsequent relapse to heavy drinking (Walter et al. 2006; Higley et al. 2011; Sinha et al. 2011).

The potential of OT as a treatment for alcohol use disorder is highlighted by a recent small clinical trial (n=11) in alcohol-dependent subjects. All subjects underwent alcohol detoxification with PRN administration of the benzodiazepine lorazepam and were concurrently randomized to intranasal OT (24 IU twice daily for 3 days) or placebo during the withdrawal period. Subjects randomized to OT had significantly fewer alcohol withdrawal symptoms and required less symptom-triggered lorazepam for withdrawal symptoms compared to placebo (Pedersen et al. 2013). Relating this finding to the early preclinical literature, the authors posit that the mechanism of this effect might relate to rapid reversal of tolerance by OT.

In the context of stress provocation using the Trier-Social Stress Test, pretreatment with a single dose of OT (40 IU) reduced stress-induced craving and anxiety in cannabis-dependent individuals (McRae-Clark- et al. 2013). This was a between-subjects double-blind placebo-controlled study (N=16) in which OT reduced marijuana craving and stress scores post-session, but did not change anxiety scores. Also using the Trier Social Stress Test, Flanagan and colleagues examined the effect of OT on the cortisol response in 31 cocaine-dependent subjects. Subjects were randomized to receive a single dose of OT (40IU) or placebo prior to the Trier Social Stress Test. There was a significant relationship between the cortisol response after social stress and the degree of adverse childhood experiences for those on placebo, which was absent in the OT group (Flanagan et al. 2015). Our group reported analogous results in cocaine-dependent in-patients, where the significant positive relationship between state anger and cue-induced craving that was observed in the placebo condition was absent in the OT condition. This was a single OT dose (24IU) crossover study in cocaine-dependent in-patients (N=23) assessing the effect of OT on desire to use, cue-induced craving, and monetary reward tasks. OT, compared to placebo, increased subjects' desire to use but had no effect on cue-induced cocaine craving (Lee, Glassman et al. 2014). .

These studies require replication as they are small and largely exploratory, with different OT dosing and patients who were all drug- or alcohol-dependent but were in different stages of treatment. Specifically, the alcoholic patients were in withdrawal, the marijuana patients were actively using, and the cocaine-dependent patients in one of the studies were abstinent and in a controlled environment. There also are no controlled studies examining the effects of OT on human drug self-administration or subjective effects in the laboratory. Clearly, more human research is needed to determine if the positive signals observed in animal models are replicated in humans. In addition, very little is known about the pharmacokinetics of OT, the effect of repeated OT dosing on behavioral outcomes over time, or the optimal dosing interval.

Brain penetrance of exogenously administered oxytocin and dosing

A key issue is whether systemically administered OT gains access to the CNS directly or whether it exerts its effects via an intermediate pathway. There is considerable controversy on the subject (Leng and Ludwig 2016). That notwithstanding, peptides have been shown to cross the blood-brain barrier, in small amounts either by extracellular active transport or by transcellular diffusion (Banks 2015). In humans, the time course of cerebrospinal fluid (CSF) levels of oxytocin and vasopressin, following their intranasal delivery, is consistent with extracellular transport, as elevated CSF levels are detected 20 −80 minutes after delivery (Born et al. 2002; Striepens et al. 2013). In similar studies, OT reached peak levels in plasma 30-40 min after intranasal administration (Lundin et al. 1986; Burri et al. 2008; Gossen et al. 2012). The relevance of circulating blood levels is unclear, given the considerable individual differences in OT peak and AUD (area under the curve) levels in plasma (Gossenet al. 2012) and the lack of correlation between plasma and CSF levels (Striepenset al. 2013; Freeman et al. 2016) . It is clear, however, that intranasal administration of OT results in elevated CSF levels of OT in humans (Born et al. 2002; Striepens et al. 2013), nonhuman primates(Chan et al. 2012; Dal Monteet al. 2014; Modi et al. 2014; Freeman et al. 2016) and rodents (Neumann et al. 2013). It is not known whether the elevation in CSF OT after systemic administration is due to the administered peptide gaining access to the CSF or whether there is a feed-forward effect stimulated by either peripheral or centrally mediated mechanisms (Ermisch et al. 1985; Carson et al. 2010). Further, it is also not clear if the delivered peptide reaches the CNS and whether it does so as an intact peptide.

The utility and feasibility of administration of intranasal OT as a medication is supported by its success in early clinical trials for the treatment of behavioral deficits associated with other neuropsychiatric disorders such as schizophrenia (Pedersen et al. 2011), social anxiety (Labuschagne et al. 2010), autism (Hollander et al. 2003), and Prader-Willi syndrome (Tauber et al. 2011). The dose of OT used has varied across studies and clinical trials. Most studies have used 24 IU OT (MacDonald et al. 2011), although 40IU OT was effective in cognition and stress studies (Ditzen et al. 2009; Simeon et al. 2011; Krueger et al. 2012; Leknes et al. 2012). Side effects of OT generally appear to be minimal. For example, a recent meta-analysis of the safety and side effects of intranasal OT, drawn from 38 randomized trials, concluded that OT produces no reliable side effects, and is not associated with adverse outcomes when delivered at 18-40 IU/dose for short-term use in controlled

research (MacDonalds et al. 2011). In addition, doses as high as 320 IU/day OT have been safely administered to human subjects, without reports of adverse events (Epperson et al. 1996; Ohlsson et al. 2005).

Conclusions and Future Directions

Clinically, OT is an attractive candidate for the treatment of substance use disorders. OT exerts effects via interactions with multiple neurotransmitter systems including, the dopamine mesolimbic reward, the HPA axis, and CRF stress systems. It also has low abuse liability, and an excellent safety profile, as well as no detectable psychoactive actions. In most human studies, subjects could not discriminate between placebo and active drug (OT) (MacDonald et al. 2011). The possibility of OT remediating social deficits in drug- and alcohol-addicted patients has been proposed given the results of studies in social-cognitive neuroscience using OT (Meyer-Lindenberg et al. 2011). Indeed, there are now multiple clinical trials underway further exploring the efficacy of OT for treatment of SUD for marijuana (NCT01827332), cocaine (NCT01573273), alcohol (NCT02407340; NCT02251912; NCT02058251), opioids (NCT02548728), and tobacco (NCT02595749). While some findings appear positive, caution should be exercised given the context- and person-dependent effect of OT (Bartz et al. 2011). Current thinking is that, in addition to its anti-stress effects, OT may facilitate the effects of dopamine (Insel, 2003), which is involved in the reinforcing properties of drugs as well as conditioned responses to drugs (Volkow et al. 2006; Lee et al. 2014). Because of this effect, exogenous OT may exacerbate some drug-related behaviors in individuals with SUD. One recent study did report that OT worsened some drug-related behaviors (Lee et al. 2014). At the same time, the growing literature over the last 30 years investigating the effect of OT on neurobehavioral responses to drugs of abuse and alcohol remains promising.

To move the field forward, several important issues must be addressed in future research. First, the mechanism of action underlying the observation of reduced drug and ethanol self-administration and reinstatement in various contexts is still unknown. Additional studies in both laboratory animal and human subjects are needed. Second, OT itself has a short half-life (Kovacs et al. 1990;, McGregor and Bowen 2012), which raises concerns of actual clinical utility. Future investigations should examine the pharmacodynamic effects of OT, which are surprisingly long in some studies. Third, given the gender differences in the OT system and in addiction-related behaviors, and the growing literature on sex-specific drug effects, it is critical that OT studies include both sexes to determine whether there are sex-specific effects. Fourth, the brain penetrance of the exogenously delivered peptide remains an unanswered question, and should be explored fully. Finally, investigations with nonpeptide OT receptor agonists are also needed as this may lead to the development of medications with longer half-life and less frequent administrations, therefore maximizing patients' treatment compliance.

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