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Targeting the Oxytocin System to Treat Addictive Disorders: Rationale and Progress to Date

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Abstract

The neuropeptide oxytocin plays a role in reward, stress, social affiliation, learning and memory processes. As such there is increasing interest in oxytocin as a potential treatment for addictions. The oxytocin system is itself altered by acute or chronic exposure to drugs of abuse. A large number of preclinical studies in rodents have investigated the effect of oxytocin on various drug-induced behaviors to determine whether oxytocin can reverse the neuroadaptations occurring with repeated drug and alcohol use. In addition, the mechanisms by which oxytocin acts to modify the behavioral response to drugs of abuse are beginning to be understood. More recently, a few small clinical studies have been conducted in cocaine, cannabis and alcohol dependence. This review summarizes the preclinical as well as clinical literature to date on the oxytocin system and its relevance to drug and alcohol addiction.

1. Introduction: function of the oxytocin system in the brain

The neurohormone oxytocin (OT), produced by the hypothalamus, has been shown to promote various social approach, bonding, maternal and stress-reducing behaviors in animals and humans [reviewed in: (1)]. OT is a nine amino acid peptide, 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. In this way OT acts as a hormone on peripheral targets to promote uterine contraction and lactation. OT is also centrally released in the brain by various mechanisms. There is dendritic release from

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the PVN and SON in the hypothalamus (2) with subsequent passive diffusion to OT receptors (OTRs) which are located throughout the brain (3). Parvocellular neurons of the PVN also produce OT and these neurons project centrally to diverse regions including the olfactory bulb, tubercule, medial and central amygdala, lateral septum, hippocampus (HC), brainstem and spinal cord among others (4). The mechanism of release from these projection neurons is beginning to be clarified, through techniques such as optogenetics, leading to a better understanding of the role of OT in local neuromodulation (4, 5). Both modes of central release, one focal and fast, the other diffuse and slow are thought to play a role in neuromodulation (6), although the faster time course is considered more compatible with the neurobiology of OT and the time course of clinical effects noted after intranasal OT administration (7). In addition, OT is an autocrine peptide that binds to its own receptors, stimulating its own release(2).

OT and the related hypophyseal nonapeptide, vasopressin (AVP; different from OT only in two amino acids) and their respective receptors are highly conserved in evolution with related peptides and receptors present in invertebrates, important in processing sensory information, associative learning and reproductive behavior (8). There is one OT receptor, cloned in 1992(9), and it belongs to the rhodopsin-type (class1) G protein-coupled receptor family. Rodent ligands (tritiated OT and iodinated OT antagonist) for the OT receptor are not selective for the human OT receptor (10), therefore the location of OT receptors in the human brain is not well worked out. Brain penetrant positron emission topography (PET) ligands for OT (11) and nonapeptide OT receptor agonists are under development (12).

Apart from its peripheral role in lactation and parturition, central OT promotes initiation of maternal behavior in virgin female rats (13, 14). In mammalian species that exhibit a monogamous social structure such as the monogamous prairie vole, who form enduring pair bonds and both males and females parent their young, central administration of OT increases pair bonding behavior in females and central administration of AVP promotes pair bonding in males of this species(15). Compared to species that are nonmonogamous, monogamous vole species have a higher density of OT receptors in the nucleus accumbens (NAc) and caudate putamen(16). In prairie voles both dopamine and OT are necessary in the NAc for partner bond formation (17). The exact nature of this interaction is not well understood, but it is thought to modulate various motivated behaviors.

Stimulation of OT projections to the VTA increases extracellular dopamine within the NAc and produces penile erection (18). Recently, OT has been shown to promote the endocannabinoid-mediated social reward processes in the NAc core(19). OT also plays a role in emotional regulation, pain and stress. Some of the neurocircuitry and mechanisms have been elucidated for these constructs. The anti-nociceptive effect of OT is blocked by naloxone and is related to potentiation of GABA interneurons in the dorsal horn (20). Axons of hypothalamic OT neurons in the central amygdala reduce neural output from the central amygdala via activation of GABA interneurons (21). The antidepressant (22) and anxiolytic (23) effects of OT are thought to be mediated by modulation of serotonergic neurocircuitry, including dorsal raphe nucleus, amygdala, HC, insula and subgenual and orbitofrontal cortex. In addition, the mechanisms by which OT acts to modify the behavioral response to drugs of abuse and ethanol are beginning to be understood. More recently, a few small

clinical studies have been conducted in cocaine, cannabis and alcohol dependence. This review summarizes the preclinical as well as clinical literature to date on the OT system and its relevance to drug and alcohol addiction. A search of the literature in PUBMED was done with key words: Oxytocin or oxytocin receptors AND Brain AND Alcohol or alcoholism or alcohol-related disorders or alcohol use disorder or ethanol or substance-related disorders. Both human and animal studies were included. There were no date or language restrictions.

2. Evidence that OT signaling is affected by drugs of abuse

The link between the OT system and addiction stems, in part, from observations of the similarity between behaviors in human addiction and social or romantic attachment (24). Moreover, there is evidence of a shared neurobiology between social affiliation and addiction, especially in affiliative species such as prairie voles. Pair-bonding has been shown to decrease the rewarding properties of psychostimulants (25); conversely, psychostimulants, have been shown to reduce affiliative behavior, suggesting that drugs may elicit a pair-bond-like response that inhibits new pair bonding (26). Prairie voles self -administer ethanol in large amounts and proximity to a familiar same sex partner buffets the tendency to increase ethanol self-administration after a period of ethanol deprivation (27). Also, in this animal model, ethanol consumption inhibits partner preference formation in males while it facilitates partner preference in females (28). There is also evidence that chronic exposure to drugs of abuse or to ethanol alters endogenous OT signaling. There is little evidence of this in humans for several reasons. First, the measurement of OT in plasma is beset by inaccurate assays which either have low sensitivity or specificity (29). Second, there is little evidence that there is a correlation between plasma and CSF levels of OT(2). Largely from preclinical literature, the overall pattern of changes appears to be a decrease in peptide expression with chronic use and an upregulation of the OT receptor. The brain regions where these changes occur is drug-specific.

2.1 Psychostimulants

Acute cocaine increased the OT level in the dorsal hippocampus (DHC)(30), an area that is responsible for contextual learning and memory involved in drug dependence(31). In contrast, chronic cocaine administration in rodents resulted in a decrease in hippocampal OT content (32) and upregulation of the OT receptor in the central amygdala (33). Chronic administration of methamphetamine (METH) to mice caused an upregulation of OT receptor density in the amygdala and hypothalamus (34). In general, although with a few exceptions, these preclinical studies show that chronic exposure to psychostimulants yielded an upregulation of OT receptor binding perhaps due to a decrease in OT peptide levels. Indeed, in human studies, plasma OT levels were lower in mothers, 1–11 months postpartum, with a history of chronic cocaine use during pregnancy compared to those with no history of cocaine use (35).

2.2 Opiates

Chronic administration of morphine to rats altered brain OT expression differentially with a decrease in OT mRNA in the SON and NAc and an increase in the VTA and locus coeruleus (36). Chronic morphine administration resulted in increased OT receptor binding in the

amygdala, piriform cortex, medial septum, and anterior olfactory nucleus; and a decrease in OT peptide levels in the hypothalamus(37).

2.3 Ethanol and Δ^9 – tetrahydrocannabinol

Ethanol administration acutely lowers plasma OT levels; indeed intravenous ethanol was used as a treatment for premature labor(38). In alcoholic individuals, plasma OT levels were decreased (39) and OT immunoreactivity was decreased in the magnocellular neurons of the hypothalamus in a post-mortem study (40). Chronic exposure to Δ^9 – tetrahydrocannabinol in rats downregulated OT mRNA expression in the NAc and VTA (41).

2.4 Ecstasy

In humans, the drug 3,4-methylendedioxymethamphetamine(MDMA) or Ecstasy produced prosocial and anxiolytic effects, the former was positively correlated with the robust increase in plasma OT levels that occurs with MDMA use (42). In rats, the subjective effects of MDMA have been shown to be dependent on OT signaling (43) and repeated MDMA resulted in an increase in hypothalamic OT mRNA (44).

2.5 Summary on the evidence that OT signaling is affected by drugs of abuse

With the exception of MDMA, while each substance has a different mechanism of action in the brain, repeated administration of each appears to reduce OT synthesis. The mechanism of this is unknown. A final common pathway of drugs and alcohol is activation of stress as well as reward processing (45). It is unknown how activation of either of these pathways results in a decrease of OT synthesis, especially when general stressors are associated with an activation of OT systems (35, 46, 47). It is also unknown if administration of exogenous OT will reverse these changes in OT synthesis and whether this would translate to reversal of addictive behaviors.

3. Evidence that OT is involved in the response to drugs of abuse

In the 1970’s Bohus and colleagues demonstrated that hypophyseal hormones modulate learning and memory with OT generally having an inhibitory effect (48). Conceptualizing addiction as a form of maladaptive learning, a subsequent large number of preclinical studies in rodents investigated the effect of OT on various drug-induced behaviors to determine whether OT could reverse the neuroadaptations occurring with repeated drug and ethanol use (32). Further studies have been done recently probing the mechanism underlying OT’s largely inhibitory effect on psychostimulant self-administration and conditioned place preference (CPP) (49–56). Recent preliminary work has also been conducted in a model of nicotine addiction. This has indicated that OT blocked withdrawal-induced elevations in somatic signs in nicotine-dependent rats but not in non-dependent rats (57).

The majority of the published literature has focused on the effects of OT on behavioral and neurochemical responses to opiates, psychostimulants and ethanol, as outlined in Tables I–III, respectively, and summarized next.

3.1 Opiates

Preclinical work on the effects of OT on opiate-related behaviors has been conducted with either morphine or heroin. A single dose of OT caused a dose dependent decrease in the development of acute and chronic tolerance to the analgesic effects of morphine. Higher doses of OT were required to reduce chronic tolerance (58–60), indicating that early tolerance is more susceptible to modification by OT. An OT receptor antagonist (OTA) reversed this effect suggesting a role for the endogenous OT system in opposing the development of acute tolerance (58, 61). OT reduced acute tolerance for morphine and the same doses of OT resulted in a dose-dependent delay in naloxone-induced withdrawal symptoms (59, 60). Intracerebroventricular (ICV) injections of OT reproduced these effects in reducing acute and chronic tolerance more potently as did direct delivery to the HC or NAc or administration of dipeptides derived from the C-terminal OT portion (60). Either single or repeated dosing of OT also inhibits tolerance to the acute and chronic analgesic effects of heroin (62). The effect of OT on heroin self-administration behavior is state dependent and is apparent only in tolerant animals where OT decreases both the acquisition and maintenance of self-administration behavior (63). The latter effect is reproduced with local injection of OT into the NAcc and HC (64). However, the effect of OT on heroin self-administration was tested with only one dose of heroin (63), therefore, without dose – response information, it is not possible to determine whether OT was inhibiting or potentiating the effects of heroin. Overall, OT administered peripherally, appears to inhibit the development of tolerance and withdrawal to opioids and this effect seems to be centrally mediated.

In a more recent study, OT administered ICV resulted in an increase in *expression* of morphine-induced CPP, with no effect on its *acquisition* (65). Morphine administration has been shown to acutely inhibit OT cell firing in the hypothalamus and repeated administration of morphine results in tolerance to this effect(66). During morphine withdrawal there was a rebound hyperexcitation of OT cells with increased release of OT (66). After conditioning with repeated injections of morphine, administration of OT may signal a withdrawal state, resulting perhaps in the increased CPP reported in this study(65). In contrast, to these results, Zanos and colleagues (37) report that the OT analogue, carbetocin, given peripherally, inhibited the development of anxiety and depressive behaviors during morphine withdrawal in addition to improving social behaviors. In the same study, the authors reported that carbetocin prevented stress induced reinstatement of CPP for morphine. These results are consistent with those from Qi and colleagues (52) who found an inhibitory effect of OT on stress primed reinstatement of CPP for METH.

3.2 Psychostimulants

Preclinical work on the effects of OT on psychostimulant-related behaviors has been conducted with cocaine, METH and amphetamine. While OT reduced tolerance to sniffing behavior and increased sensitization to the locomotor effects of cocaine (67, 68), only the largest dose used in the study had a significant effect on these behaviors. Larger doses of OT reduced locomotor hyperactivity and stereotyped behaviors induced by both cocaine (69–71) and METH(50, 51), but not amphetamine(32, 60). Of note for these experiments is the long duration of action of a single dose of OT administered subcutaneously on locomotor

hyperactivity, i.e. up to 2 hours(69). This pharmacodynamic effect is not understood as this duration of effect is considerably longer than one would expect from a peptide with a half-life of minutes in the plasma (72) and ~20 minutes in the cerebrospinal fluid(73). That said, there is no information on the half-life of the peptide in brain tissue.

Zhou and colleagues examined the effect of OT on cocaine self administration under various conditions as well as cue- and drug-primed reinstatement of cocaine- and sucrose- seeking behavior (74). OT dose-dependently reduced cocaine self-administration under conditions of increasing motivational demands (fixed ratio schedules of 1 and 5 and progressive ratio paradigms). OT reduced the breakpoint for cocaine self-administration under a progressive ratio schedule. The peptide also reduced the effects of cocaine or cue priming on reinstatement of cocaine self-administration behavior after extinction(74). Accompanying reinstatement, the reductions in the bed nucleus of the stria terminalis of phosphorylated ERK and GluA1 were reversed by OT as was the reduction of pERK in the prefrontal cortex (PFC) (74). While the effect of OT on primed reinstatement extended to sucrose self-administration, these molecular changes were evident only in the cocaine primed reinstatement group. This suggests that reduction of protein phosphorylation may be a potential mechanism by which OT reduces psychostimulant reinforcing behaviors.

More recent work on OT and psychostimulants is with METH delivering OT ICV. OT reduces METH-induced locomotor hyperactivity(51), and in a further microdialysis study (75), the authors examined the effect of OT on METH-induced changes in extracellular glutamate and γ-aminobutyric acid (GABA) levels in the medial prefrontal cortex (mPFC) and dorsal hippocampus (DHC), both regions involved in the development of METH addiction. OT administration did not affect basal glutamate levels, but blunted the METH-induced glutamate increase in the mPFC and inhibited METH-induced glutamate decrease in the DHC via down regulation of the NR1 subunit of the NMDA receptor in the mPFC and upregulation of the glutamatergic transporter (GLT1) in the DHC. OT also caused increased basal GABA levels in mPFC and DHC, and blunted METH-induced GABA decrease in DHC, suggesting that OT acts as an inhibitory neuromodulator in these brain regions.

OT also reduces the *acquisition*, not *expression* of METH-induced CPP (52) which is opposite to that reported with morphine (65). This suggests that OT interferes with the rewarding effect of METH and less to inhibit memory retrieval processes. With respect to reinstatement, both stress and cue (not drug primed) reinstatement of METH-CPP is decreased by OT (52, 56, 76). In the study by Qi and colleagues (52), the dissociation between OT's effect to reduce stress (not drug-primed) reinstatement of CPP for METH was accompanied by differences in medial prefrontal cortical (mPFC) glutamate levels as measured by microdialysis. There was no significant increase in glutamate levels in the mPFC after METH-primed reinstatement, however, there was an increase in glutamate levels after stress-primed reinstatement that was reduced by OT and this effect was reversed by OTA. In further work by the same group (56), this effect of OT on stress priming of CPP reinstatement was explored by microinjecting OT into the DHC and mPFC, given the importance of these regions as sites of OT modulation of the glutamatergic response to METH (75). Reinstatement after restraint stress was inhibited by OT injected into the mPFC and this was reversed with OTA. It was also inhibited when injected into the DHC, albeit at a

higher dose and the effect was not reversed by OTA. Han and colleagues (56) also examined downstream signaling pathways known to be involved in METH addiction and found that OT reversed the activity of NR2B–CaMKII–CREB pathway in the mPFC and the deficit of ERK–CREB pathway in the DHC via its receptor during the stress-priming METH-induced CPP reinstatement.

Overall, OT appears to exert its effect on psychostimulant-induced behaviors via modulating glutamatergic and GABA-ergic pathways in limbic areas. Its effect to reduce stress induced reinstatement of METH induced CPP is a consistent finding across studies (52, 56). For drug primed reinstatement of METH seeking behavior, local injections into the subthalamic nucleus (77) and NAc core (78) reduce drug seeking behavior. These effects have not been tested for cocaine.

3.3 Alcohol

A recent report showed that a single dose of OT delivered centrally attenuated the sedative and ataxic effects of ethanol. This effect was mediated by the $GABA_A$ receptor, not the OT receptor (79). In contrast, a single dose of OT had no effect on the development of tolerance; rather, repeated dosing prior to ethanol resulted in reduced tolerance to the hypothermic response to ethanol(80, 81). Vasopressin had the opposite effect(82), that is, to increase tolerance formation to ethanol. Interestingly, once tolerance developed, administration of OT had no effect on tolerance(80). Similarly, in ethanol naïve or ethanol dependent mice, a single dose of OT had no effect on the severity of picrotoxin-induced seizures (83). OT, administered before ethanol daily, resulted in milder ethanol withdrawal seizures precipitated by picrotoxin (83), suggesting rapid reversal of tolerance. Large doses of OT, administered peripherally as well as centrally, had no effect on ethanol drinking using a two-bottle free-choice paradigm (84). However, McGregor and Bowen (85) found a long lasting effect of OT administration on ethanol preference in rats. Indeed, a single dose of OT, 1 mg/kg, produced a progressive reduction in preference for the ethanol-containing beverage as compared to non-ethanol-containing sweet solution that lasted up to six weeks. Also, 10 days treatment with OT, 1mg/kg, 2 weeks before the start of a two-bottle free-choice paradigm provided evidence that there was significantly lower ethanol preference in OT treated compared to control rats. Finally, modulation of OT receptor with administration of the OT receptor agonist carbetocin or genetic over-expression of OT receptors via a lentiviral vector in NAc resulted in reduced acquisition and ethanol-primed reinstatement of CPP as well as increased rates of extinction(53).

Overall, studies to date suggesting that OT plays a role in reversing tolerance and reducing in an enduring way, alcohol preference, hold promise for OT as a potential treatment for alcohol use disorders both acutely to manage withdrawal and chronically to reduce the rewarding effects of alcohol.

4. Brain penetrance of Oxytocin

There are several lines of evidence indicating that systemically administered OT exerts its effects centrally to mediate behaviors relevant to addiction. Early studies showed that OT administered peripherally in rodents reduces the behavioral effects induced by

psychostimulants such as locomotor hyperactivity and sniffing (69–71) and self administration(32). Central OT administration in smaller doses reproduced these effects OT(51, 71). Central administration of an OT receptor antagonist reversed these effects(51, 52, 71). More recently, Carson and colleagues administered OT peripherally and found reduced locomotor hyperactivity, self-administration and reinstatement of drug seeking behavior (49, 50). The duration of the increase in locomotor hyperactivity was 80 minutes which is longer than the window indicated by the peptide's half-life. These behavioral changes were accompanied by central changes: a reduction in the METH-induced c-Fos expression in subthalamic nucleus and NAc core (50). When OT was administered without METH, there was an increase in c-Fos in PVN and SON of the hypothalamus where OT is synthesized, suggesting a feed-forward effect. These studies are important as they demonstrate that peripheral administration of OT results in central modulation of brain regions that are activated by METH. It is unclear as to whether systemically administered OT gains access to the CNS directly or whether it exerts its effects via an intermediate pathway. Peptides have been shown to cross the blood brain barrier, albeit in small amounts either by extracellular active transport or by transcellular diffusion(86). Given the time course of studies reporting CSF levels of peptides following intranasal delivery of nonapeptides, where elevated CSF levels are detected 20 –80 minutes after delivery, extracellular transport seems more likely(87, 88). Relevant to human research, intranasal administration of OT results in elevated CSF levels of OT in humans (88), nonhuman primates (89) and rodents(7). Open questions are if the delivered peptide reaches the CNS and if so, whether it does as an intact peptide.

5. Human Studies of intranasal OT in Alcohol and Drugs of Abuse

To date, there have been only a few studies performed in human subjects with alcohol and drug dependence that have investigated the effects of OT. Overall each of these studies focuses on a different substance with subjects in different states of abstinence, and administers OT either with a single dose challenge or with repeated administration. In this way, there are no results across studies in drug or alcohol dependence for comparison.

Pedersen and colleagues (90) reported a small study of alcohol dependent patients (n = 11) who were admitted to an inpatient unit for alcohol detoxification and were randomized to intranasal OT (24 IU twice daily for 3 days) or placebo. OT was significantly more effective than placebo in decreasing alcohol withdrawal symptoms and OT-treated patients required less symptom triggered lorazepam for withdrawal symptoms (90). The authors posit that the mechanism of this effect might relate to rapid reversal of tolerance by OT. In a between-subject double-blind placebo-controlled study, a single OT (40 IU) dose reduced stress-induced craving in cannabis-dependent individuals (n = 16) using the Trier-Social Stress Test as a stress provocation (91). Additionally, OT reduced marijuana craving and stress scores, not anxiety scores. It also decreased the change in dehydroepiandrosterone (DHEA) levels compared to placebo from pre- to post-Trier Social Stress Test. In another study using the Trier Social Stress Test in 31 cocaine-dependent subjects (92), the significant relationship between stress-induced cortisol levels and adverse childhood experiences present in those assigned to placebo was absent for those assigned to receive a single dose of OT (40 IU) prior to stress induction. In a group (n = 65) of regular MDMA users OT's (20

IU) prosocial effects correlated with subjects' prosocial response to MDMA (93). Our group recently reported a single OT dose (24 IU) crossover study in cocaine dependent inpatients (n = 23) assessing OT's effect on desire to use, cue induced craving, monetary reward tasks and social cognition tasks (94). OT, compared to placebo, increased subjects' desire to use but had no effect on cue induced craving. A positive significant relationship between state anger and cue induced craving was observed in the placebo but not in the OT group. On OT, performance on monetary reward and social cognition tasks increased and decreased, respectively compared to placebo.

These small studies are exploratory and require replication. The dosing of OT, the treatment seeking status, state of withdrawal, and outcome measures were completely different across the studies. The alcoholic patients were in withdrawal, the marijuana patients were actively using and non-treatment seeking, and in one of the two studies with the cocaine dependent patients, participants were court-ordered to a controlled environment. With the exception of the MDMA study, the only common factor for the cocaine, cannabis and alcohol studies was that subjects had a diagnosis of dependence on their respective drugs of choice.

6. Conclusion

When considering OT as a putative treatment for addictions in light of the preclinical and clinical literature reviewed here, there are many factors that can influence the effect of OT on compulsive drug use, that is, type of drug, stage of addiction, and length of sobriety or abstinence, if any. As we see from the preclinical literature presented here, the results vary widely as a function of these factors. For example, with respect to the effect of OT to reduce tolerance, repeated administration of OT prior to cocaine (68) or ethanol (80) is required for the effect. In fact, for ethanol, one dose of OT or the administration of OT once tolerance was established, produced no effect on tolerance(80). In contrast, for opiates, a single dose before or after tolerance was established, was sufficient to reduce opiate tolerance to analgesia (62). Although tolerance is not necessary or sufficient for drug or alcohol dependence, the reversal of tolerance is important for the period of withdrawal and the effect of OT on this reversal seems to be drug- and context- dependent. For self-administration of opiates, unlike ethanol, OT reduces self-administration only if tolerance is present (63). The effect of OT on CPP is inconsistent across substances: there is a decrease in acquisition of the conditioned behavior for ethanol (53) and psychostimulants (52) but no effect for morphine (65). OT seems to increase the expression of CPP when administered after the acquisition of CPP has been established. This finding and our results (94) is what is predicted from the vole literature. As OT may facilitate the effects of dopamine (95), which is involved in the reinforcing properties of and cue reactivity to drugs (96), exogenous OT could exacerbate drug-related behaviors in dependent individuals. The possibility of using OT as a treatment for addiction outside of the treatment of withdrawal is based on several factors. OT is not itself rewarding. Doses that are associated with CPP are much higher than that used in humans (97) and in most human studies, subjects cannot discern that they have received the drug (98). That said, a recent rodent study showed that OT injected into the central amygdala resulted in CPP as well as anxiolytic effects (99). There are deficits in OT functioning in addiction that may be remediated by administration of OT, particularly if it is given in a therapeutic context. OT might shift salience to reinforce social stimuli in drug

dependent patients who forsake social ties in favor of drug use. Social support is a prominent feature of drug rehabilitation programs. OT has been shown to reduce stress when given in the contest of social support(100). This stress buffering effect could also be beneficial in addiction treatment given the importance of stress as a cause for relapse. The effect in rodents of a single or repeated dosing of OT alone to reduce ethanol preference on a long term basis, i.e., 6 weeks, after the OT dose (85), has implications for its use in controlled treatment settings where it may be useful to reduce relapse after discharge.

In addition to playing a role in treatment of alcohol use disorders, OT may also play a role during adolescence to prevent the development of alcohol and psychostimulant use disorders. Bowen and colleagues(101) demonstrated that OT, administered systemically to male rats during early adolescence for 10 days, reduced *ad libitum* consumption of "beer" during early adulthood without affecting water intake. Rats who were administered OT also showed reduced anxiety behaviors and had increased levels of hypothalamic OT mRNA and a trend toward increased plasma levels of OT. In a similar study with METH, analogous results were found in female rats after adolescent pretreatment with OT. The latter was associated with reduced self-administration of METH in adulthood, reduced METH-primed drug seeking behavior and higher plasma OT levels(102). This suggests not only that the endogenous OT system may play a role in the neuroplastic changes that occur with repeated psychostimulant and ethanol exposure but that exogenous OT may buffet these changes and prevent the development of alcohol and psychostimulant use disorders as well as anxiety disorders. The corticotropin-releasing factor (CRF) antagonist properties of OT (103) may provide a way to target the negative reinforcement that maintains addiction. Finally, while OT itself has a short half-life and some studies (69) (85) highlight the importance of future investigations on the pharmacodynamic effects of OT, investigations with non-peptide OT receptor agonists may lead to the development of medications with longer half-life and less frequent administrations, therefore maximizing patients' compliance to the treatment.

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Appendix

Table I

Summary of the effects of oxytocin on opiate-induced behaviors

Behavior	Effect	OT dose (per animal or / kg)	Route	Interval OT→Opiate (minutes)	Opiate dose	Species	OT repeated	OT ICV**	OTA reverses effect	Site of action	Reference
MORPHINE											
Acute tolerance to analgesia	↓	0.0005, 0.005*, 0.05*, 5*,50* μg	sc	60	100 mg/kg	mice	No	Yes	Yes	ns	(58, 59)
Chronic tolerance to analgesia	↓	0.5,5.0,50*, 100*μg	sc	120	pellet 37.5 mg sc	mice	No	Yes	ns	HC, NAc	(59, 60)
Withdrawal (naloxone)	delay	0.5,5.0,50*, 100*μg	sc	120	pellet 37.5 mg sc	mice	No	Yes	ns	HC, NAc	(59, 60)
Anxiety, Depression post withdrawal	↓	Carbetocin 6.4mg/kg	ip	Post 7d withdrawal	20mg/kg→100mg/kg/day x 7 d	mice	No	ns	ns	ns	(37)
Social behaviors post withdrawal	↑										
Conditioned Place Preference(CPP):											

Behavior	Effect	OT dose (per animal or / kg)	Route	Interval OT→Opiate (minutes)	Opiate dose	Species	OT repeated	OT ICV**	OTA reverses effect	Site of action	Reference
Acquisition	↔	0.2μg or OTA alone	icv	5	5mg/kg sc	rats	Dailyx 3d	ns	ns	ns	(65)
Expression	↑	0.2μg	icv	n/a	5mg/kg sc		No	ns	No	NAc shell	(65)
Reinstatement by stress	↓	Carbetocin 6.4mg/kg	ip	n/a	n/a	mice	n/a	ns	ns	ns	(37)
HEROIN											
Tolerance to analgesia:											
Single dose	↓	2–200μg/kg day1 or 4	sc	60	800μg/kg	mice	No	ns	ns	ns	(62)
Repeated doses	↓	2–200μg/kg		60	800μg/kg		Dailyx 4d		ns	ns	(62)
Self-administration:											
Heroin naïve	↔	0.5μg	sc	60	0.02mg/ infusion	rats	Dailyx 8d	ns	ns	ns	(63)
Heroin tolerant											
Acquisition	↓	0.5*μg	sc	60	0.02mg/ infusion	rats	Dailyx 8d	ns	ns	ns	(63)
Maintenance	↓	0.05, 0.5*, 5.0* ug	iv	60	0.02mg/ infusion	rats	No	ns	ns	NAc; HC***	(63, 104)

↓= Decreased; ↑= Increased; ↔= no effect; *= dose producing significant effect; OT=oxytocin; OTA=OT receptor antagonist; sc=subcutaneous; ip=intraperitoneal; icv= Intracerebroventricular; iv=intravenous; HC=hippocampus; NAc=Nucleus Accumbens; n/a=not applicable

Carbetocin: OT analogue; d: day; ** results reproduced with icv OT administration; *** Duration of effect=24h; ns: not studied

Table II

Summary of the effects of oxytocin on psychostimulant-induced behaviors

Behavior	Effect	OT Dose (Per animal or /kg)	Route	OT→Psychostimulant Interval (minutes)	Dose Psychostimulant	Species	OT repeated	Central effect	OTA reversed	Reference
Locomotor hyperactivity (familiar environment)	↓	0.2,1.0* and 5.0* μg	sc	60	Cocaine 30 mg/kg, sc	mice	No	ns	ns	(69)
	↔	0.5,5.0,50μg	sc	60	AMPH 1mg/kg, sc	mice	No	ns	ns	(60)
	↓	2 mg/kg OT	ip	10	METH: 2mg/kg, ip	rats	No	↓meth induced cfos expr. in subthalamic nucleus +NACC core	ns	(50)
	↓	0.1,0.5*,2.5*μg	icv	30	METH 2mg/kg, ip	mice	No	Reduced DA utilization in striatum	Yes	(51)
Exploratory activity (Novel environment)[Δ]	↓ inverted U	0.005,0.05*,0.5*,1.0*, 5.0 μg	sc	60	Cocaine 7.5 mg/kg, sc	mice	No	ns	ns	(70)
Stereotyped behavior/sniffing	↓	0.5,1.0 μg	sc	60	Cocaine 15 mg/kg, sc	rats	No	ICV, 100pg to NAcc, olfactory tubercle**	Yes	(71)
	↔	0.5,5.0,50 μg	sc	60	AMPH 1mg/kg, sc	rats	No	ns	ns	(32)
Sensitization (locomotor effects)[§]	↑	0.005,0.05,0.5*μg	sc	60	Cocaine 7.5 mg/kg, sc twice daily x 5 d	mice	Dailyx 5d	ns	ns	(67)
Tolerance (sniffing) familiar environment	↓	0.005,.05 *μg[&]	sc	60	Cocaine 7.5 mg/kg, sc twice daily x 4 d	rats	Dailyx 4d	Ventral HC	ns	(67, 68)
Self- administration	↓	.5 μg	sc	60	Cocaine	rats	No	ns	ns	(32)
	↓	0.001, 0.01, 0.1, 0.3, 1*mg/kg	ip	30	METH 0.1mg/kg/infusion	rats	Dailyx 5d	ns	ns	(49)
FR 1	↓	0.1, 0.3*, 1*, 3* mg/kg	ip	30	Cocaine 0.2mg/infusion	rats	No	ns	ns	(74)
FR 5	↓	1 mg/kg	ip	30	Cocaine 0.2mg/infusion	rats	No	ns	ns	(74)
PR	↓	1 mg/kg		30	Cocaine 0.2mg/infusion	rats	No	ns	ns	(74)
Reinstatement drug seeking			ip	30		rats	No	OT normalizes ↓p- ERK in PFC and BNST; ↓p-GluA1 in BNST	ns	(74)
Cue primed	↓	0.1, 0.3, 1* mg/kg			n/a					
Drug primed	↓	0.1, 0.3*, 1* mg/kg			Cocaine 10 mg/kg					
Conditioned Place Preference: Reinstatement	↓stress prime	0.5, 2.5 μg	Central sites		METH 2mg/kg ip	mice	No	mPFC> DHC	Yes	(56)
	↓ Stress prime	0.1*,0.5*,2.5*μg	icv	30	METH 1mg/kg	mice	No	↓glu levels in mPFC induced by stress priming	Yes	(52)
	↔Drug prime									
	↓Cue prime	10 ng OT	icv	5	n/a	rats	No	ns	Yes	(76)

Behavior	Effect	OT Dose (Per animal or /kg)	Route	OT→Psychostimulant Interval (minutes)	Dose Psychostimulant	Species	OT repeated	Central effect	OTA reversed	Reference
Conditioned Place Preference (CPP)										
Acquisition	↓	0.1,0.5,2.5*μg	icv	30	METH 2mg/kg ip	mice	No	ns	Yes	(52)
Expression	↔									
Acquisition	↓	0.6mg 0.6ng	ip ic	10	METH 1mg/kg ip	rats	No	STh or NAcc core	ns	(55)
Extinction CPP	↑	0.1*,0.5*,2.5*μg	icv	30	METH 2mg/kg	mice	No	ns	ns	(52)
Reinstatement drug seeking	↓	1mg/kg	ip	30	METH 1mg/kg ip	rats	No	ns	ns	(49)
Adolescent Exposure to OT	No effect tested	1mg/kg	ip	Postnatal days 28–37	None	Rats female	Yes	ns	ns	(102)
Self- administration PR	↓			Adulthood	METH 0.1mg/kg/infusion				ns	(102)
Drug Primed Reinstatement METH seeking	↓			Adulthood	METH 1mg/kg ip				ns	(102)
Drug Primed Reinstatement METH seeking	↓	0.2–3.6 *pmol	STh	5	METH 1mg/kg ip	rats	No	STh	No	(77, 78)
		0.5*,1.5*,4.5* pmo Dose dependent(77)	NAc core					NAc core		

OT=oxytocin; DA=dopamine; AMPH=amphetamine; METH=methamphetamine; OTA=oxytocin receptor antagonist

PFC=Prefrontal Cortex; BNST=Bed Nucleus Stria Terminalis; PR=progressive ratio; FR1=fixed ratio schedule 1; FR5= fixed ratio schedule 5; ↓= Decreased; ↑= Increased; ↔= no effect; * dose producing significant effect; OTA=OT receptor antagonist; sc=subcutaneous; ip=intraperitoneal; icv= Intracerebroventricular; HC=hippocampus; NAc=Nucleus Accumbens; p-ERK= phosphorylated extracellular signal-regulated kinase; p-GluA1= phosphorylated glutamate receptor subunit A1; mPFC= medial prefrontal cortex; DHC=dorsal hippocampus; Glu= Glutamate; STh=Subthalamic Nucleus; Carbetocin=OT analogue; d= day; ns=not studied; $^{\Delta}$No effect of OT on novel environment alone; ** No effect in Caudate nucleus, central amygdala, olfactory nucleus; §Non-familiar environment; $^{\&}$OT alone in repeated doses, had no effect on sniffing or locomotor hyperactivity measures of the test dose of cocaine.

Table III

Summary of the effects of oxytocin on ethanol-induced behaviors

Behavior	Effect	OT Dose (Per animal or /kg)	Route/Site	Species	OT→ETOH interval	ETOH dose	OT Repeated	Central effect	Context/state Dependent	Reference
Tolerance to hypothermic effect of Ethanol	↔	Single dose, day 1	sc	mice	120min	4g/kg, ip	No	ICV +500x more potent	No effect if OT injected after tolerance developed Environmental cues for Ethanolnecessary for OT effect	(80–82, 105)
	↓hypothermic response	2*, 1*,0.5*, 0.25, 0.02, 0.002 IU					Dailyx3d			
Motor impairment	↓sedation, ataxia	1 μg/5μl	icv	rats	immediate	1.5g/kg, ip	No	Yes	ns	(79)
Adult Alcohol consumption	↓ alcohol consumption ↓anxiety ↑sociability	1 mg/kg, ip	ip	rats	n/a	Lickometer 4.44%Ethanol	Daily on post- natal days 33-42	ns	ns	(101)
Ethanol preference	↓preference Ethanolx 6 weeks duration	0.3 or 1mg/kg x 1 dose	ip	"P"rats	2 days	Lickometer 5%Ethanol vs 3%Sucrose	No	ns	ns	(85)
	↓preference Ethanol	1mg.kg			10 days		Dailyx10d			
Ethanol consumption	↔	OT 10 mg/kg 0.5μg	ip icv	mice	10 min	2, 4, 6 and 8% Ethanol;2-bottle choice	Dailyx15d	ns	psychosocial stress	(84)
CPP for Ethanol	↓acquisition ↑extinction ↓Ethanol- primed reinstatement	Carbetocin NAc OTR overexpression in NAc	n/a	mice	15 min	2g/kg, 10%Ethanol,ip	Dailyx7d	Yes	ns	(53)

↓=Decreased; ↑= Increased; = no effect; *= dose producing significant effect; OTA=OT receptor antagonist; sc=subcutaneous; ip=intraperitoneal; icv= Intracerebroventricular; NAc=Nucleus Accumbens; OT= oxytocin; n/a= not applicable; CPP= Conditioned Place Preference; OTR= oxytocin receptor

Carbetocin= OT analogue; d= day; min=minutes; ns= not studied.

Keypoints

1. The neuropeptide oxytocin plays a role in reward, stress, social affiliation, learning and memory processes as well as behaviors related to drugs of abuse and alcohol.
2. The oxytocin system is itself altered by acute or chronic exposure to drugs of abuse and alcohol.
3. Oxytocin administration may reverse the neuroadaptations occurring with repeated drug and alcohol use and as such may be a putative treatment for addictions.