



Review

Breaking the loop: Oxytocin as a potential treatment for drug addiction

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ABSTRACT

Drug use typically occurs within a social context, and social factors play an important role in the initiation, maintenance and recovery from addictions. There is now accumulating evidence of an interaction between the neural substrates of affiliative behavior and those of drug reward, with a role for brain oxytocin systems in modulating acute and long-term drug effects. Early research in this field indicated that exogenous oxytocin administration can prevent development of tolerance to ethanol and opiates, the induction of stereotyped, hyperactive behavior by stimulants, and the withdrawal symptoms associated with sudden abstinence from drugs and alcohol. Additionally, stimulation of endogenous oxytocin systems is a key neurochemical substrate underlying the prosocial and empathogenic effects of party drugs such as MDMA (Ecstasy) and GHB (Fantasy). Brain oxytocin systems exhibit profound neuroplasticity and undergo major neuroadaptations as a result of drug exposure. Many drugs, including cocaine, opiates, alcohol, cannabis, MDMA and GHB cause long-term changes in markers of oxytocin function and this may be linked to enduring deficits in social behavior that are commonly observed in laboratory animals repeatedly exposed to these drugs. Very recent preclinical studies have illustrated a remarkable ability of exogenously delivered oxytocin to inhibit stimulant and alcohol self-administration, to alter associated drug-induced changes in dopamine, glutamate and Fos expression in cortical and basal ganglia sites, and to prevent stress and priming-induced relapse to drug seeking. Oxytocin therefore has fascinating potential to reverse the corrosive effects of long-term drugs abuse on social behavior and to perhaps inoculate against future vulnerability to addictive disorders. The results of clinical studies examining intranasal oxytocin effects in humans with drug use disorders are eagerly awaited.

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Introduction

The idea that oxytocin may be involved in addiction-relevant behaviors has been discussed for many years (e.g. Kovacs et al., 1998; Sarnyai and Kovacs, 1994), and is an idea that is currently undergoing

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a major resurgence (Baskerville and Douglas, 2010; McGregor et al., 2008; Sarnyai, 2011). This has included a realization that the acute prosocial effects of some popular recreational drugs most likely involve stimulation of oxytocin systems (Dumont et al., 2009) and that the neural substrates of social bonding and drug reward may be intertwined (Liu et al., 2011; Young et al., 2011b). At the same time, there is mounting preclinical evidence that oxytocin might serve as a novel treatment for drug and alcohol abuse (e.g. Carson et al., 2010a) with an attendant interest in oxytocin from clinicians dealing with addicted clients.

As these clinicians will attest, people with drug and alcohol problems often display antisocial traits and exhibit poor decision making in the social domain (Dawe et al., 2009; Volkow et al., 2011). It is possible then that some of the corrosive effects of drug abuse on the brain involve drug-induced modifications to the neural substrates of affiliative behavior, including brain oxytocin systems (e.g. Silva et al., 2002; Sivukhina et al., 2006). Drug users may become “bonded” to their drugs and to the drug-related cues that envelop their lives, often to the exclusion of other forms of reward, including other human beings (Edwards and Self, 2006; Kalat, 1978; Robinson and Berridge, 1993; Schiorring, 1981).

On the other hand, stable social bonds and happy relationships, perhaps associated with higher levels of oxytocin (Feldman et al., 2007; Grewen et al., 2005; Seltzer et al., 2010), might be protective against addiction to drugs (Blackson and Tarter, 1994; Bowen et al., 2011; Johnson and Pandina, 1991; Liu et al., 2011). It is perhaps not surprising then that the few effective treatments promoting recovery from addictions appear to have a magic “X” factor that comprises some form of social rehabilitation or social reintegration. For example, it may be that the social support provided by Alcoholics Anonymous meetings causes therapeutic success by resetting dysfunctional oxytocin pathways (Koerner, 2010).

In the current review we will probe these issues and provide an update on the possible roles of oxytocin in addiction-relevant behaviors, and the emerging potential of oxytocin as a novel pharmacotherapy for addictive disorders.

Oxytocin mediates the acute prosocial effects of party drugs

MDMA (“Ecstasy”) is a fascinating drug characterized by its capacity to engender strong feelings of love and closeness towards other people, increased trust, and greater openness to the views and feelings of others. These powerful prosocial actions of MDMA in humans are replicated in animal models. For example, in unfamiliar pairs of rats meeting for the first time, MDMA markedly reduces aggression and increases a behavior known as adjacent lying (Kirilly et al., 2006; Morley and McGregor, 2000; Thompson et al., 2007). This rat “cuddling” is reminiscent of the increased social contacts in a variety of animal species given oxytocin, oxytocin analogs, or oxytocin receptor agonists (Goodson et al., 2009; Lukas et al., 2011; Witt et al., 1992). Oxytocin receptor antagonists provoke a reciprocal loss of preference for social stimuli (Lukas et al., 2011).

It was therefore natural to ask whether MDMA-induced social facilitation in rats might involve oxytocin. MDMA and its metabolites stimulate hypothalamic oxytocin release *in vitro* (Forsling et al., 2002). Accordingly, *in vivo* MDMA was shown to powerfully induce Fos expression in the oxytocin-releasing neurons in the supraoptic nucleus (SON) and paraventricular nucleus (PVN) of the hypothalamus, leading to dose dependent increases in plasma oxytocin, and activation of forebrain neural circuits known to regulate affiliative behavior (Thompson et al., 2007, 2009). Importantly, the prosocial effects of MDMA in rats were significantly attenuated by an oxytocin receptor antagonist (Thompson et al., 2007). Furthermore, MDMA pre-treatment leads to lasting increases in OTR mRNA in the hypothalamus which may be related to long-term social interaction deficits caused by the drug (van Nieuwenhuijzen et al., 2010).

The powerful prosocial effects of MDMA in humans (Bedi et al., 2009, 2010) are also associated with elevated peripheral oxytocin levels (Dumont et al., 2009; Wolff et al., 2006). Strikingly, the subjective prosocial feelings induced by MDMA in humans more closely track plasma oxytocin levels than plasma MDMA levels (Dumont et al., 2009). A role for oxytocin in the subjective effects of MDMA is further underlined by findings that the oxytocin antagonist atosiban interferes with MDMA, but not amphetamine, appropriate responding in rats trained to discriminate these drugs from placebo (Broadbear et al., 2011). The oxytocin analog carbetocin partially generalized to the MDMA training cue, suggesting that oxytocin receptor activation is a primary element of MDMA’s subjective effects.

High ambient temperatures, and dehydration, increase oxytocin release (Uvnas-Moberg et al., 1993) which could further amplify the oxytocinergic effects of MDMA and its subsequent social and neural effects. Accordingly, MDMA’s prosocial, neural and rewarding effects appear to be facilitated in rats under high ambient temperatures (Cornish et al., 2003; Hargreaves et al., 2007) and this interaction might explain the tendency for humans to take MDMA under hot and dehydrating conditions (Parrott, 2004). Hyponatremia (low plasma sodium) is a condition frequently caused in humans by MDMA (Budisavljevic et al., 2003), and is associated with increases in peripheral oxytocin levels and social affiliation in rodents (Krause et al., 2011). More specifically, numerous studies have demonstrated that the SON and PVN are activated in response to osmotic and volemic thirst and that this results in secretion of OT into the bloodstream (McKinley et al., 1994; Miyata et al., 2001; Shibuki et al., 1988). Perhaps animals must lose their fear of other animals when visiting communal watering places, and so control of osmolality and sociability may coincide in the actions of oxytocin in the SON (Krause et al., 2011).

MDMA is a potent releaser of 5-HT, and the oxytocin-dependent prosocial effects of MDMA in both humans and rats appear linked to a cascade in which 5-HT release impacts on hypothalamic 5-HT_{1A} receptors, leading to oxytocin release. The 5-HT containing terminals and the OT-containing cell bodies in the SON and PVN share close proximity (Emiliano et al., 2006) and 5-HT_{1A} receptors are localized on the perikarya of magnocellular oxytocin containing neurons (de Souza Villa et al., 2008; Marvin et al., 2010). Accordingly, MDMA-like prosocial behavior in rats is mimicked by the 5-HT_{1A} receptor agonist 8-OH-DPAT, with these prosocial effects attenuated by an oxytocin receptor antagonist (Thompson et al., 2007). Further, in rats, the 5-HT_{1A} antagonist WAY 100,635 blocked both the prosocial effects and heightened oxytocin release caused by MDMA (Thompson et al., 2007) as well as associated MDMA-induced SON activation (Hunt et al., 2011).

Oxytocin and the prosocial effects of other drugs

Another popular dance party drug, gamma-hydroxybutyrate (GHB), is similarly prosocial to MDMA, with potent anti-aggressive, anxiolytic as well as other prosocial properties (Pedraza et al., 2007; Schmidt-Mutter et al., 1998; Sumnall et al., 2008). GHB, like MDMA, causes strong activation of oxytocinergic circuitry in the SON and PVN (Van Nieuwenhuijzen et al., 2009). Indeed, GHB was once used to promote uterine contractions in childbirth, suggestive of a powerful oxytocin-like tocolytic effect (Geldenhuys et al., 1968). We have found that the new popular party drug mephedrone (4 methylmethcathinone, “Meow”) also causes substantial SON and PVN activation, and this might conceivably explain the intense prosocial and entactogenic effects inherent in user reports of this emerging dance party drug (Motbey et al., 2011).

Oxytocinergic effects of other popular drugs are less well established. Alcohol is perhaps the most commonly used “party drug”, but it appears to inhibit, rather than stimulate, peripheral oxytocin and vasopressin release (Gibbens and Chard, 1976; Subramanian,

1999). Of course peripheral oxytocin levels can be a rather poor proxy for central oxytocin actions, and it is therefore possible that central oxytocin systems are stimulated by alcohol, perhaps by releasing central oxytocin circuits from the reciprocal inhibition caused by vasopressin (Huber et al., 2005). This could be usefully addressed in future studies using microdialysis to examine central oxytocin and vasopressin release during voluntary alcohol consumption.

On the other hand, not all drugs that strongly stimulate oxytocin release are necessarily prosocial. Lithium is a potent stimulator of hypothalamic oxytocinergic circuitry (Cui et al., 2001), and while a useful treatment for a number of psychiatric conditions, is not frankly prosocial in its effects. The relationship between oxytocin and antidepressant action could also use further clarification: similar to MDMA the action of SSRI, SNRI and tricyclic antidepressants on SERT and 5-HT_{1A} receptors will most likely stimulate oxytocin and such actions could conceivably underlie the utility of these drugs in conditions such as social anxiety disorder and depression (Rotzinger et al., 2010; Uvnas-Moberg et al., 1999). Indeed, the low plasma levels of oxytocin seen in depressed cohorts (Scantamburlo et al., 2007) might be rebalanced by SSRI and other antidepressant actions. Indeed, powerful antidepressant-like and anxiolytic effects of oxytocin and oxytocin receptor agonists are evident in animal models (Chavarras et al., 2010; Grippo et al., 2009; Ring et al., 2010; Rotzinger et al., 2010).

The PVN and SON are by no means social-specific structures and are engaged by dehydration, stress, food intake and a host of other environmental stimuli. The use of new tools such as transgenic rats that express fluorescence when magnocellular neurons are activated (Katoh et al., 2010, 2011) will help better define the microcircuitry and projections of the SON and PVN that are specific to social stimulation.

Oxytocin, social reward and drug reward

Although oxytocin is clearly involved in the prosocial effects of some drugs, it is not clear whether oxytocin itself is rewarding. Intranasal oxytocin administration to humans is not euphorogenic, and is typically not discriminated from placebo by recipients, despite modulation of social cognition (Macdonald et al., 2011). One study in rats reported a conditioned place preference with systemically administered oxytocin, suggesting reward, yet this involved an extremely high dose (8 mg/kg) (Liberzon et al., 1997). Current indications are that oxytocin is in little danger of becoming an abused drug in its own right, although the poor brain penetration and short half-life of the peptide itself may contribute to this. It would be of interest to determine whether more potent, orally bioavailable, non-peptide oxytocin agonists (e.g. Ring et al., 2010) have abuse potential, perhaps analogous to MDMA or benzodiazepines.

The existing literature suggests that oxytocin amplifies the reinforcing properties of social engagement, perhaps priming social reward rather than providing the reward itself. For example, rodent studies show that MDMA-induced activation of key forebrain reward sites such as the nucleus accumbens, and affiliative sites such as the medial preoptic area, is far greater when the drug is given under social conditions (Thompson et al., 2009). Similarly, human brain imaging studies indicate that MDMA decreases amygdala response to angry faces while increasing the ventral striatal response to happy faces (Bedi et al., 2009). Social cognition is thus biased towards positive social cues by oxytocin, although the story is by no means simple (Bartz et al., 2011).

An impressive body of work conducted with prairie and meadow voles indicates that oxytocin interacts with dopamine at the level of the ventral striatum to regulate social processes such as pair bonding as well as drug reward (Liu et al., 2011; Young et al., 2011a). Not only do drug reward and social reward involve similar pathways but it appears also that animals with more evolved social reward systems (such as monogamous prairie voles) may be differentially sensitive

to drug reward (Anacker and Ryabinin, 2010). Forming a strong bond with a partner, at least in voles, may indeed decrease vulnerability to the rewarding effects of stimulants (Liu et al., 2011).

However, the exact interaction between dopamine and oxytocin in regulating drug and social reward is complex and poorly understood, and may vary according to behavioral context (Baskerville and Douglas, 2010). So while dopamine (through D2 receptors) and oxytocin work together in the ventral striatum to “cement” partner preferences in monogamous species (Liu and Wang, 2003), oxytocin may inhibit dopamine in the same region to diminish drug reward. For example, we recently reported that methamphetamine-induced Fos expression in the nucleus accumbens core, but not shell, was significantly reduced by oxytocin (Carson et al., 2010b), consolidating previous research findings that oxytocin reduces methamphetamine-induced dopamine efflux in the accumbens (Qi et al., 2008). Lithium – a drug that increases oxytocin release in rodents (Cui et al., 2001) – also prevents methamphetamine-induced Fos expression in the nucleus accumbens (Lee et al., 1999).

Oxytocin: switching from inanimate towards animate rewards

The environment of most animals contains both social and non-social reinforcers. At any given moment an animal can decide to seek social interaction with conspecifics or to pursue the rewards inherent in “objects”, be they toys, computers, foodstuffs or drugs. Might there be parallel brain circuits for social and non-social rewards, with oxytocin increasing the incentive motivational properties of social relative to non-social stimuli? While oxytocin stimulates appetite in breastfeeding infants (with breastfeeding itself a form of social engagement for both infant and mother), it generally decreases appetite for both food and water “objects” in the adult animal (Olson et al., 1991; Verty et al., 2004) while priming social and sexual motivational systems (Melis and Argiolas, 2011).

Extreme dopaminergic stimulation, in the absence of oxytocin, may produce intense object-orientated behaviors, as shown in stimulant-induced stereotypy in laboratory animals. The phenomenon of “punding” seen in heavy methamphetamine users, and Parkinsonian patients treated with dopaminergic agonists, refers to compulsive performance of repetitive, mechanical tasks, such as assembling and disassembling objects or, collecting, sorting or cleaning household objects (Fasano and Petrovic, 2010; Gescheidt and Bares, 2011). Intense stereotypy and fascination with mechanical objects is also characteristic of autism: oxytocin treatment can help break such stereotypy (Hollander et al., 2003; Sala et al., 2011). It is also striking that oxytocin receptor knockout mice display impairments in behavioral flexibility (Sala et al., 2011).

It might be hypothesized then that excessive dopamine acting in basal ganglia circuits might bias behavior towards object-orientated rewards and execution of habitual behavioral loops. With the additional stimulation of oxytocin, as is obtained with drugs such as MDMA and GHB, the bias is perhaps tilted towards an intense focus on social stimuli, which may be coupled by an abrupt termination of object-orientated behaviors. This might constitute an important and sudden switching of behavioral modes from frenetic execution of object-orientated behavioral loops into a mode of social engagement.

Porges (2003) speaks of the neural substrates of a social engagement system in which brain circuitry used for defensive freezing is co-opted to facilitate the passive, non-defensive immobility, and parasympathetic dominance that is characteristic of social engagement. The ventrolateral periaqueductal gray, which is rich in oxytocin receptors, is seen as a major node in this network. High doses of oxytocin are known to cause sedation and immobility in rodents which is coupled to anxiolytic and prosocial effects (Uvnas-Moberg, 1998). In the infant, such a system facilitates the passivity required to feed, and fosters a sense of relaxation and contentment. This is polar opposite to the sympathomimetic, hyperactive, manic state that is induced by stimulant drugs.

“Breaking the loop”: acute effects of oxytocin on drug self-administration

The suggestion that oxytocin might provide an exit strategy from the narrow “behavioral loops” that characterize compulsive drug taking is supported by a number of observations in preclinical research. The seminal research by Sarnyai et al., provided important early signs of oxytocin's efficacy in this regard. Exogenously administered oxytocin in rodents decreased the hyperactivity, locomotor sensitization and stereotyped behaviors caused by cocaine (Sarnyai, 1998) and inhibited the self-administration of opiates in rats (Ibragimov et al., 1987; Kovacs and Van Ree, 1985).

More recently, intracerebroventricular (ICV) oxytocin inhibited methamphetamine-induced place preference, facilitated the extinction of methamphetamine-induced CPP and prevented its stress-induced reinstatement in mice (Qi et al., 2009). Mechanistically, this was linked to oxytocin inhibiting the enhanced dopamine utilization in the striatum caused by methamphetamine, recapitulating earlier findings that oxytocin antagonizes cocaine-induced increases in dopamine utilization in the nucleus accumbens (Kovacs et al., 1990). Additionally, oxytocin inhibited prefrontal glutamate release during stress-induced reinstatement of methamphetamine place preference (Qi et al., 2008) with subsequent observations that oxytocin attenuates addiction-related changes in NMDAR1 expression in the prefrontal cortex (Yang et al., 2010).

These important findings were consolidated by findings that oxytocin (0.3–1 mg/kg IP) powerfully inhibits intravenous methamphetamine self-administration in rats (Fig. 1A) (Carson et al., 2010a) and diminishes the capacity of non-contingent methamphetamine “primes” to reinstate methamphetamine-seeking behavior in abstinent rats. Fos immunohistochemistry revealed that systemic oxytocin significantly reduced methamphetamine-induced neuronal activation in the nucleus accumbens core, and the subthalamic nucleus (Fig. 1B). The subthalamic nucleus is often seen as a key component in the

circuitry underlying compulsive behaviors, and has recently been targeted with deep brain stimulation as a means of alleviating severe obsessive compulsive disorder and modifying the aforementioned “punding” behavior caused by dopamine agonists in Parkinson's disease (Klavriv et al., 2009; Mallet et al., 2008; Pallanti et al., 2010). We have also recently shown that systemic oxytocin, or microinjections of oxytocin directly into the accumbens core, or subthalamic nucleus, can reduce the CPP produced by methamphetamine in rats (Baracz et al., 2012).

As well as reducing methamphetamine-induced Fos expression in key brain regions, systemically administered oxytocin (2 mg/kg) strongly activates oxytocin-positive cells in the supraoptic nucleus (Fig. 1C), consistent with earlier suggestions of a feed-forward effect of oxytocin on its own dendritic release, akin to “self-stimulation” (Ludwig and Leng, 2006; Rossoni et al., 2008). Repeated systemic oxytocin treatment to rats self-administering methamphetamine also resulted in chronically increased plasma levels of oxytocin, suggestive of a long-lasting upregulation of endogenous oxytocinergic systems (Fig. 1D). Systemically administered oxytocin also activated other central sites including the central amygdala, lateral parabrachial nucleus and the locus coeruleus as had been similarly reported in earlier Fos studies involving ICV oxytocin administration (Kita et al., 2006; Popeski and Woodside, 2001).

Other recent work from our laboratory examined the interaction between oxytocin and alcohol self-administration in rats. This follows on from earlier observations that co-administered oxytocin inhibits the tolerance to the hypothermic and ataxic effects of alcohol in animal models (Jodogne et al., 1991; Kovacs et al., 1998; Szabo et al., 1987; Tirelli et al., 1992). Initially, we examined how oxytocin affected consumption of a sweet alcohol-containing beverage that is popular with young Australians (*Raspberry Vodka Cruiser*, 5% ethanol v/v). Alcohol-preferring “P” rats were given a choice between this beverage and a non-alcoholic sweet solution (3% sucrose) in daily sessions in a “lickometer” apparatus (Hargreaves and McGregor, 2007). Strikingly,

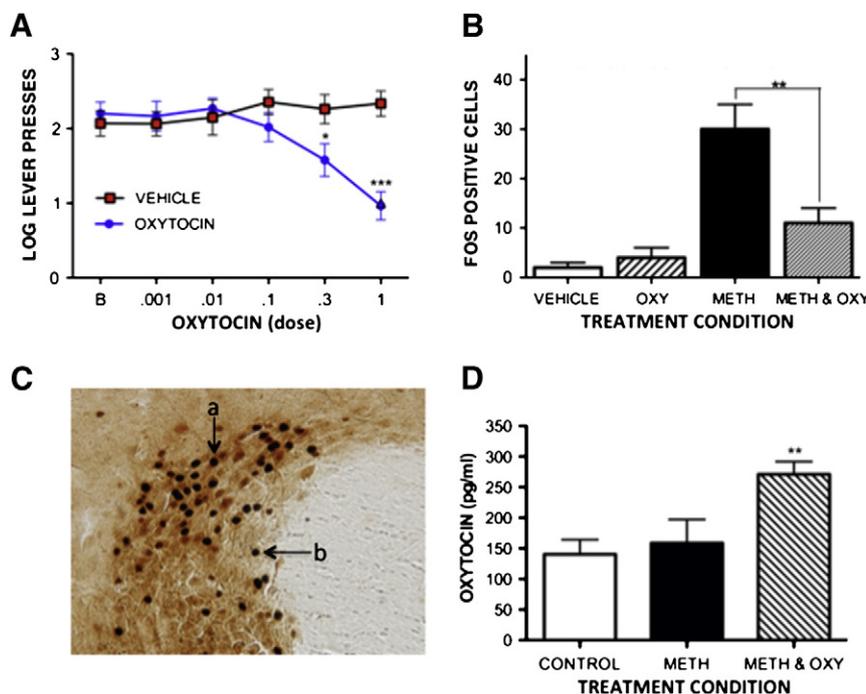


Fig. 1. (A) Peripherally administered oxytocin (doses on x-axis) reduces lever pressing for intravenous METH in rats (Carson et al., 2010a). (B) Peripherally administered oxytocin (2 mg/kg) reduces METH-induced activation of the Subthalamic Nucleus (Carson et al., 2010b), and (C) Peripheral oxytocin (2 mg/kg) activates oxytocin-positive neurons in the Supraoptic Nucleus (Carson et al., 2010b). Arrows (a) and (b) show examples of single labeled (Fos only) and double labeled (Fos and oxytocin) cells respectively. (D) Rats given intermittent IP oxytocin treatment show increased plasma oxytocin 2 weeks after treatment. Fig. 1D shows mean (+SEM) blood plasma concentration (pg/ml) from an ELISA (Assay Designs Oxytocin EIA kit 900–153) conducted on plasma collected from the experimental cohort from Carson et al. (2010a). Plasma was collected 14 days after the cessation of a 19 day dosing period during which time rats self-administering methamphetamine received either 7 doses of IP oxytocin from 0.001 to 1 mg/kg (METH and OXY) or equivalent IP injections of vehicle (METH). CONTROL rats did not self-administer methamphetamine and received no oxytocin. ** = $P < 0.01$, *** = $P < 0.001$.

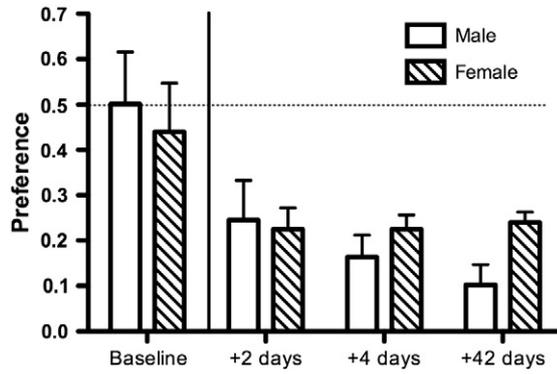


Fig. 2. (A) Lasting reduction in “Vodka Cruiser” preference (relative to 3% sucrose) in male and female “P” rats following two IP doses of oxytocin prior to test sessions (0.3 and 1 mg/kg).

a single administration of oxytocin (1 mg/kg) resulted in a long lasting-decline (at least 6 weeks) in the preference for the alcoholic beverage relative to sucrose (Fig. 2). Long-term overall intake of fluid was not affected by oxytocin treatment although there was a moderate decline in the intake of both beverages immediately following acute treatment. To rule out an explanation of this lasting effect in terms of conditioned taste aversion, we uncoupled oxytocin administration from alcohol presentation by giving rats repeated doses of oxytocin (1 mg/kg, IP) for 10 days prior to initiating access to alcohol two weeks after the final oxytocin dose was administered. Here, a remarkably low preference for the alcoholic beverage was evident in oxytocin pre-treated rats. These provocative findings with alcohol, while striking, require further exploration and validation. For example, oxytocin knockout mice consume greater amounts of sweet solutions than wild types (Amico et al., 2005) and it would clearly be of interest to examine whether they also display excessive levels of alcohol consumption.

An anti-alcohol effect of oxytocin might also invite a possible reinterpretation of the therapeutic efficacy of baclofen in treating alcohol use disorders. Baclofen, a GABA_B agonist that is often used to treat spasticity, has a striking ability to inhibit alcohol craving and this has led to major worldwide interest and clinical trials of this substance for alcohol use disorders, albeit with some mixed results (Addolorato et al., 2011; Ameisen, 2011; Garbutt et al., 2010; Liu and Wang, 2011). We have documented that high doses of baclofen, and GHB, both potently stimulate the supraoptic nucleus in rats, most likely leading to increased levels of oxytocin (Van Nieuwenhuijzen et al., 2009). It is therefore possible that the ability of baclofen to inhibit alcohol and other drug craving rests on an indirect action on oxytocin.

Oxytocinergic effects might also be relevant to the anti-craving effects of GHB, which is licensed in Italy for the treatment of alcohol withdrawal and craving (Caputo, 2011; Leone et al., 2010). These suggestions are worthy of further investigation and might further

consolidate the potential efficacy of oxytocin-based therapeutics for alcohol use disorders.

Neuroadaptations in oxytocin during the development of addiction and tolerance to drugs

Chronic drug use causes lasting neuroadaptations that can drive compulsive drug seeking and neurocognitive and personality changes in habitual drug users. Brain oxytocin systems display profound neuroplasticity in response to a variety of environmental and pharmacological stimuli and in relation to developmental milestones such as puberty, pregnancy and parturition (Kramer et al., 2006; Lukas et al., 2010; Neumann, 2007; Slattery and Neumann, 2008). Accumulated studies suggest that repeated exposure to drugs of abuse causes long-term social deficits and neuroadaptations in various markers of oxytocin function (summarized in Table 1). For the most part, the changes seen are consistent with a loss of oxytocinergic function and a possible rebound increase in oxytocin-related mRNA transcription and receptor expression.

As Table 1 summarizes, chronic ethanol exposure caused degeneration of oxytocin containing magnocellular neurons in the hypothalamus of both humans and rats (Silva et al., 2002; Sivukhina et al., 2006). Chronic morphine decreases brain oxytocin synthesis (You et al., 2000), while cocaine administration decreased hippocampal, preoptic and hypothalamic oxytocin levels (Elliott et al., 2001; Johns et al., 1993; Sarnyai, 1998). Repeated low-dose tetrahydrocannabinol (THC) (the main psychoactive ingredient of cannabis) downregulated oxytocin receptor expression and diminished oxytocin innervation in the nucleus accumbens of rats (Butovsky et al., 2006). It is notable here that chronic cannabinoid exposure causes lasting social deficits in rats (O’Shea et al., 2004, 2006; Quinn et al., 2008). Eight weeks after repeated MDMA or GHB treatment, rats had increased oxytocin mRNA expression (with MDMA) or oxytocin receptor mRNA expression (with GHB) in the hypothalamus, as well as showing blunted social behavior (van Nieuwenhuijzen et al., 2010). Overall, these findings are suggestive of major neuroadaptations in oxytocin systems occurring with a wide range of recreational drugs, yet more work needs to be done to better characterize such drug-related changes and to more clearly link regional changes in brain oxytocin levels, oxytocin and oxytocin receptor gene expression, oxytocin receptor density and altered sociability. Then, there is also the important issue of how vasopressin systems might adapt as a result of drug and alcohol exposure.

If neuroadaptations caused by repeated exposure to drugs of abuse involve endogenous oxytocin pathways, then administration of exogenous oxytocin may have potent effects in reversing these effects. Indeed, the social withdrawal caused by subchronic PCP administration is reversed by intra-amygdala administration of oxytocin (Lee et al., 2005) or by vasopressin V_{1a} agonists (Matsuoka et al., 2005). Systemic oxytocin was also able to reverse the PPI deficits induced by NMDA antagonists suggesting antipsychotic potential

Table 1
Oxytocin-related neuroadaptations following chronic exposure to drugs.

Species	Treatment	Finding	Reference
Human	Alcoholics	Decreased supraoptic OT-containing neurons <i>post mortem</i>	Sivukhina et al., 2006
Rat	Alcohol (repeated)	Decreased hypothalamic OT-containing neurons	Silva et al., 2002
Rat	Alcohol/nicotine (gestational)	Decreased VTA and MPO OT in dams. Increased VTA OT in adolescent offspring; decreased VTA OT in adult offspring. Increased OTR binding in NAc males adult offspring.	McMurray et al., 2008
Rat	Cocaine (acute)	Decreased hypothalamic, hippocampal and MPO OT	Elliott et al., 2001; Johns et al., 1993; Johns et al., 2010; Sarnyai, 1998
Rat	GHB (repeated)	Increased hypothalamic OTR mRNA	van Nieuwenhuijzen et al., 2010
Rat	MDMA (repeated)	Increased hypothalamic OT mRNA	van Nieuwenhuijzen et al., 2010
Rat	Morphine (repeated)	Decreased OT synthesis	You et al., 2000
Rat	THC	Diminished OT immunoreactivity in NAc	Butovsky et al., 2006

Abbreviations: OT = oxytocin, OTR = oxytocin receptor, VTA = ventral tegmental area, MPO = medial preoptic area, NAc = nucleus accumbens.

(Feifel and Reza, 1999). This potential role for oxytocin in rescuing animals from drug-induced antisocial tendencies is clearly worthy of further examination. Assessment of plasma oxytocin and vasopressin levels in drug abusing populations might also be a useful approach for clinical studies. A recent study from our group failed to find any difference in plasma oxytocin or vasopressin levels in current methamphetamine users meeting DSM IV criteria for dependence, but uncovered blunted cortisol levels (Carson et al., under review). These participants, however, were not tested in the drug-free state, and future studies will hopefully obtain analogous results for dependent populations during withdrawal and abstinence.

Might oxytocin “inoculate” against future vulnerability to drug abuse?

In the therapeutic setting, maintenance of long-term abstinence is clearly the biggest therapeutic hurdle in treating addictions. Oxytocin clearly has acute inhibitory effects on the intake of alcohol, opiates and stimulants, but might it also change the brain in a way that causes lasting changes in the disposition to consume drugs and alcohol? The well-characterized anxiolytic and prosocial effects of oxytocin are more apparent with repeated, rather than acute, administration. For example, chronic, but not acute, oxytocin attenuated the pathological high anxiety of female rats selectively bred for high anxiety-related behavior (Slattery and Neumann, 2010) and repeated oxytocin treatment had lasting positive effects on blood pressure, pain tolerance and corticosterone levels (Holst et al., 2002; Petersson et al., 1996, 1999; Uvnas-Moberg, 1998). This stimulation of oxytocin receptors triggers increased dendritic and peripheral release of oxytocin which further stimulates oxytocin receptors establishing a positive feedback loop resulting in hypertrophy of the oxytocinergic neurons, decreased astrocytic coverage of neurons, and a subsequent increase in juxtaposition of neurons at the level of somas and dendrites across the entire oxytocin system (for a review see Theodosis, 2002). Ultimately, this process results in a lasting increase in the productivity and functionality of the oxytocin system, the duration of which can last for months depending on the magnitude and length of the stimulation. If oxytocin modulates the attractiveness of drug-related reward, then such upregulation may be protective against addictive behaviors.

A recent study from our laboratory (Bowen et al., 2011) provided intriguing preliminary evidence that giving adolescent rats repeated exposure to exogenous oxytocin over a short period during adolescence can have subtle yet significant effects that last into adulthood. These behavioral and neural changes included: reduced anxiety; increased sociability; inhibition of the development of alcohol consumption (see Fig. 3); increased oxytocin in plasma; and altered OTR mRNA in the hypothalamus. This is of particular interest as it indicates again that short-term oxytocin treatment causes lasting behavioral changes consistent with long-term abstinence and psychological wellbeing. Upregulation of oxytocin production following treatment with exogenous oxytocin (Fig. 1D) may be a key factor in changing the “state” of the addicted individual.

These findings warrant further mechanistic exploration of the processes stimulated by oxytocin that promote altered dispositions towards drugs and alcohol. As noted above, it could be the case that oxytocin is shifting people away from the drug-related “object” oriented pursuits, and towards interpersonal relationships. This would lead to a series of accumulating positive changes that make the individual stronger, more socially integrated, and less susceptible to drug abuse and associated psychopathologies.

Oxytocin as a candidate therapeutic for acute drug withdrawal/detoxification

The preclinical results discussed above offer hope for the objective of using oxytocin to cause lasting reductions in drug craving and drug abuse. However, other intriguing evidence also speaks to the ability of oxytocin to ameliorate physical and behavioral effects associated with acute drug withdrawal. In seminal preclinical studies oxytocin was shown to reduce the severity of withdrawal after chronic high dose administration of opiates (Kovacs et al., 1998) and ethanol (Szabo et al., 1987). A further key study indicated that the withdrawal symptoms arising from sudden precipitated cannabinoid abstinence in rats were reversed by administration of lithium, via an OT-dependent mechanism (Cui et al., 2001). In an analogous fashion, symptoms arising from naloxone-precipitated withdrawal from morphine in mice were attenuated by co-administration of lithium via an OT-dependent mechanism (You et al., 2001).

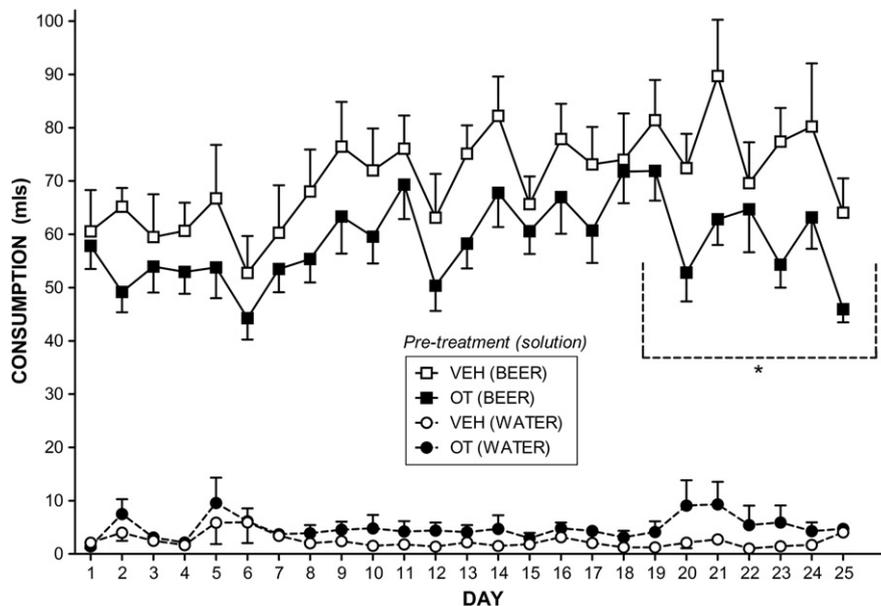


Fig. 3. Repeated daily oxytocin pretreatment (1 mg/kg \times 10 days) was given to male adolescent Wistar rats. Some 30 days later they were given *ad libitum* access to beer (Toohey's New, 4.5% ethanol) in their home cages over a 25 days period with water also available. A subtle but significant reduction in beer intake was seen in the oxytocin pre-treated rats. From Bowen et al. (2011).

These findings have prompted preliminary trials of lithium in treating cannabis withdrawal with encouraging results (Winstock et al., 2009), and such trials could conceivably be extended to future examination of intranasal oxytocin or other oxytocin-releasing compounds as therapeutics. There is also an ongoing clinical trial examining the efficacy of add-on intranasal oxytocin treatment during acute alcohol withdrawal treated with lorazepam (ClinicalTrials.gov Identifier: NCT01212185) the results of which are certain to be illuminating.

Corticotropin-releasing factor (CRF) is a major determinant of dysphoria during drug withdrawal, and CRF antagonists have well-documented effect in blocking withdrawal-induced anxiety and drug-seeking behavior in rodent models (Logrip et al., 2011). Oxytocin has marked inhibitory effects on CRF-related activation of the hypothalamic pituitary adrenal axis and forebrain (Dabrowska et al., 2011; Windle et al., 2004) and powerful anxiolytic and antidepressant-like effects, as discussed above. This is clearly worth consideration as a primary mechanism through which oxytocin may ameliorate withdrawal symptoms during detoxification. The ability of oxytocin to perhaps inoculate against future drug use, and rebalance affiliative brain processes, suggests that former drug users might emerge from the clinic following oxytocin-assisted detoxification with an augmented chance of achieving long-term abstinence.

Conclusions and future directions

The nexus between oxytocin and addiction has reached a fascinating stage of development with evidence coming from diverse sources that speaks to the role of the social neuropeptide in addiction-relevant behaviors. The early work by Kovacs et al. showing that oxytocin can prevent physiological tolerance to opiates, cocaine and alcohol, was an important departure point illustrating the ability of the neuropeptide to inhibit addiction-related neuroadaptations in mesolimbic and forebrain sites (Sarnyai, 2011). A corollary of this is that the endogenous oxytocin system is downregulated as a result of drug abuse and that such adaptations might drive not only tolerance, but also disinhibition of drug seeking behavior and a loss of interest in social rewards (McGregor et al., 2008). These predictions have been supported by newer preclinical evidence for anti-craving and inoculation-like effects of exogenous oxytocin on drug-seeking behavior, although elucidation of specific neuroadaptations underlying these effects requires further endeavor. Nonetheless, it has certainly reached the stage where clinical trials of intranasal oxytocin in drug-dependent populations are warranted, and it is hoped that such studies will occur sooner rather than later.

The unfavorable physiochemical and pharmacokinetic properties of oxytocin itself may limit its clinical use, and the future of oxytocin-based therapeutics for addiction may well rest with novel oxytocin receptor agonists such as WAY 267,464 (Hicks et al., under review; Ring et al., 2010). Even then, there are safety issues with respect to the ability of oxytocin receptor agonists to do what nature always intended oxytocin to do: stimulate uterine contractions and the milk let down reflex. This may limit the therapeutic potential of oxytocin-based therapeutics, particularly in drug-dependent females of childbearing age.

There are also interesting philosophical issues to consider relating to the ability of repeated oxytocin treatment to sculpt personalities and proclivities: do we want to reach a stage where human teenagers are given oxytocin to reduce their future likelihood of drug abuse? What will the world look like if everyone takes oxytocin? Might people become dependent on high potency novel oxytocin ligands to regulate their own social behavior and to find social interaction adequately rewarding? We can only speculate about such matters. However, one thing remains clear: the study of oxytocin in relation to addiction is positioned at a very exciting stage.

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