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REVIEW

From ultrasocial to antisocial: a role for oxytocin in the acute reinforcing effects and long-term adverse consequences of drug use?

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Addictive drugs can profoundly affect social behaviour both acutely and in the long-term. Effects range from the artificial sociability imbued by various intoxicating agents to the depressed and socially withdrawn state frequently observed in chronic drug users. Understanding such effects is of great potential significance in addiction neurobiology. In this review we focus on the 'social neuropeptide' oxytocin and its possible role in acute and long-term effects of commonly used drugs. Oxytocin regulates social affiliation and social recognition in many species and modulates anxiety, mood and aggression. Recent evidence suggests that popular party drugs such as MDMA and gamma-hydroxybutyrate (GHB) may preferentially activate brain oxytocin systems to produce their characteristic prosocial and prosexual effects. Oxytocin interacts with the mesolimbic dopamine system to facilitate sexual and social behaviour, and this oxytocin-dopamine interaction may also influence the acquisition and expression of drug-seeking behaviour. An increasing body of evidence from animal models suggests that even brief exposure to drugs such as MDMA, cannabinoids, methamphetamine and phencyclidine can cause long lasting deficits in social behaviour. We discuss preliminary evidence that these adverse effects may reflect long-term neuroadaptations in brain oxytocin systems. Laboratory studies and preliminary clinical studies also indicate that raising brain oxytocin levels may ameliorate acute drug withdrawal symptoms. It is concluded that oxytocin may play an important, yet largely unexplored, role in drug addiction. Greater understanding of this role may ultimately lead to novel therapeutics for addiction that can improve mood and facilitate the recovery of persons with drug use disorders.
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Abbreviations: AVP, arginine vasopressin; GHB, gamma-hydroxybutyrate; L-368,899, (2S)-2-Amino-*N*-[(1S,2S,4R)-7,7-dimethyl-1-[[[4-(2-methy lphenyl)-1-piperazinyl]sulphonyl]methyl]bicyclo[2.2.1]he pt-2-yl]-4-(methylsulfonyl)butanamide; MDMA, 3,4,-methylenedioxymethamphetamine; NAS, nucleus accumbens; OT, oxytocin; PVN, paraventricular nucleus of the hypothalamus; SON, supraoptic nucleus; THC, delta-9-tetrahydrocannabinol; TOC, tocinoic acid; WAY 100,635, *N*-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-*N*-2 pyridinylcyclohexanecarboxamide maleate salt; VTA, ventral tegmental area; 8-OH-DPAT, 8-hydroxy-2-(di-n-propylamino)-tetraline

Introduction

The social causes and social consequences of drug use, and their underlying neural correlates, are important but as yet understudied areas in the study of addiction. Even the most cursory reflection on human drug use suggests that the motivation to consume drugs is inextricably linked to the social context. Obvious examples are the widespread use of alcohol for 'social lubrication', the popular use of 'party drugs' such as 3,4-methylenedioxymethamphetamine (MDMA) (Ecstasy) and gamma-hydroxybutyrate (GHB) for their prosocial and prosexual effects, and drug initiation in adolescence as a result of 'peer pressure'. Drug use may even define social groups, with the psychedelic movement of the 1960s and rave phenomenon of the late 1980s and 1990s seeing entire subcultures identified by their drug choice and drug-induced behaviours.

The adverse consequences of drug use are often expressed in terms of costs to society; encapsulating the idea that repeated drug use entails profound social costs. Familiar examples include the random violence inflicted by intoxicated pub patrons, the aggressive psychosis and paranoia

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seen in heavy crystal methamphetamine users, the poor parenting of drug addicted parents and the disintegrating social life and resulting isolation of compulsive drug users. Some 80% of prisoners have a history of drug abuse and most are incarcerated for antisocial acts related to or committed under the influence of licit or illicit drugs (see for example, Dolan *et al*., 2007). Most people detained by police test positive for one or more drugs of abuse in the 24 h following arrest (Mouzos *et al*., 2006). Moreover, psychiatric diagnoses of social dysfunction such as borderline personality disorder and antisocial personality disorder are over-represented in drug abusing populations (Brady *et al*., 2007; van den Bosch and Verheul, 2007).

Untangling the genetic, environmental, epigenetic, pharmacological and neural determinants of social breakdown consequent to drug use is a major undertaking in addiction neurobiology and a task that has barely started. Part of the problem is that the neural and genetic determinants of social behaviour remain obscure, with the fledgling area of 'social neuroscience' having only recently emerged (for example, Caldu and Dreher, 2007; Sanfey, 2007). Another problem has been that animal models of drug addiction, which are the cornerstone of basic research in addiction neurobiology, rarely take social factors into account. Experiments typically involve rats or mice self-administering a drug under solitary conditions and frequently such animals are housed individually to prevent damage to chronically indwelling catheters or to allow clear assessment of individual drug or alcohol intake. Nonetheless, occasional preclinical studies of social factors in drug abuse make clear the social implications of acute intoxication (for example, Miczek *et al*., 2004; Pedraza *et al*., 2007; Thompson *et al*., 2007), and the adverse social consequences of repeated drug exposure (for example, Morgan *et al*., 2002; Clemens *et al*., 2007).

In the present review, we review the general ideas that (1) commonly used drugs of abuse exert major acute effects on sociability, (2) repetitive drug use may cause lasting adverse neuroadaptations in key neural substrates subserving social behaviour and (3) both of the above processes may involve the 'social' neuropeptide oxytocin (OT).

Oxytocin: the social neuropeptide

Oxytocin is the most abundant neuropeptide in the hypothalamus and is best known in mammalian species for the characteristic peripheral effects that it promotes, including uterine contractions during parturition and milk ejection during lactation (for review see Gimpl and Fahrenholz, 2001). The neurosecretory cells of the supraoptic nucleus (SON) and paraventricular nucleus of the hypothalamus (PVN) are the main sites in the brain in which OT is synthesized, and these cells release OT and the closely related neuropeptide arginine vasopressin (AVP), via the posterior pituitary into the bloodstream to produce peripheral actions (see Figure 1). Independently of this, the SON and PVN also release OT and AVP from their dendrites and cell bodies and this OT diffuses locally within the hypothalamus, and presumably over much larger distances to influence a wide network of central OT receptors (Landgraf and Neumann, 2004; Ludwig and Leng, 2006; Neumann, 2007). Limbic and brainstem regions also receive direct innervation of OT and AVP positive fibres from the parvocellular PVN. Local release of OT has been documented in sites such as the amygdala, septum and bed nucleus, particularly in relation to stress and defensive behaviours (see for example, Ebner *et al*., 2005) and such OT release may depend upon such direct projections from the PVN or perhaps as yet undocumented extrahypothalamic OT-containing cell bodies in these regions (Neumann, 2007). OT receptors are to be found in many sites that are relevant to drug seeking behaviour, including the nucleus accumbens, ventral tegmental area, bed nucleus of the stria terminalis, central amygdala, medial amygdala, hippocampus and ventral pallidum (Vaccari *et al*., 1998).

Correlating central OT release with behavioural changes via techniques such as microdialysis involves considerable technical challenges (Neumann, 2007). Measuring changes in peripheral OT in plasma is accomplished much more readily, but only gives an imperfect index of the complexities of central oxytocin release. An increasing number of experimental conditions have been documented in which blood OT levels are uncorrelated with central OT levels and our understanding of the dynamics and determinants of central OT release are rudimentary at best (Neumann, 2007).

Despite this, there is compelling evidence that OT acts in the brain to promote a variety of vital adaptive responses, including maternal behaviour, the formation of monogamous pair-bonds, sexual arousal and orgasm, peer to peer social interaction, social memory and anxiety reduction (Keverne and Curley, 2004; Storm and Tecott, 2005; Lim and Young, 2006; Neumann, 2007). These functions are highlighted not only from microdialysis studies but also from those in which behaviour has been observed following administration of OT receptor antagonists. Other important evidence comes from OT (OTKO) or OT receptor (OTR-KO) knockout mice, with these mutants showing various deficits in social behaviour, maternal behaviour, social recognition and an anxious and aggressive phenotype (Winslow *et al*., 2000; Winslow and Insel, 2002; Ragnauth *et al*., 2005; Takayanagi *et al*., 2005; Pedersen *et al*., 2006; but see also Crawley *et al*., 2007).

Recent studies also highlight remarkable anxiolytic and prosocial effects of intranasally administered OT in humans, including increased 'trust', decreased amygdala activation towards fear-inducing stimuli, improved recognition of social cues and increased gaze directed towards the eye regions of others (Kirsch *et al*., 2005; Kosfeld *et al*., 2005; Domes *et al*., 2006; Guastella *et al*., 2008). This has generated immense current interest in the role of OT in human psychopathologies such as autism, schizophrenia and social phobia (Carter, 2007; Heinrichs and Gaab, 2007; Hollander *et al*., 2007; Schulkin, 2007) and a growing realization that OT and AVP may play a key role in social and other processes relating to drug intoxication and drug addiction (Zhou *et al*., 2008).

AVP inhabits many of the same neural locations as OT. However in contrast to OT, AVP tends to promote aggression, defensiveness and fear (Ebner *et al*., 2005; Huber *et al*., 2005). Blockade of central AVP type V_{1b}, receptors (nomenclature in

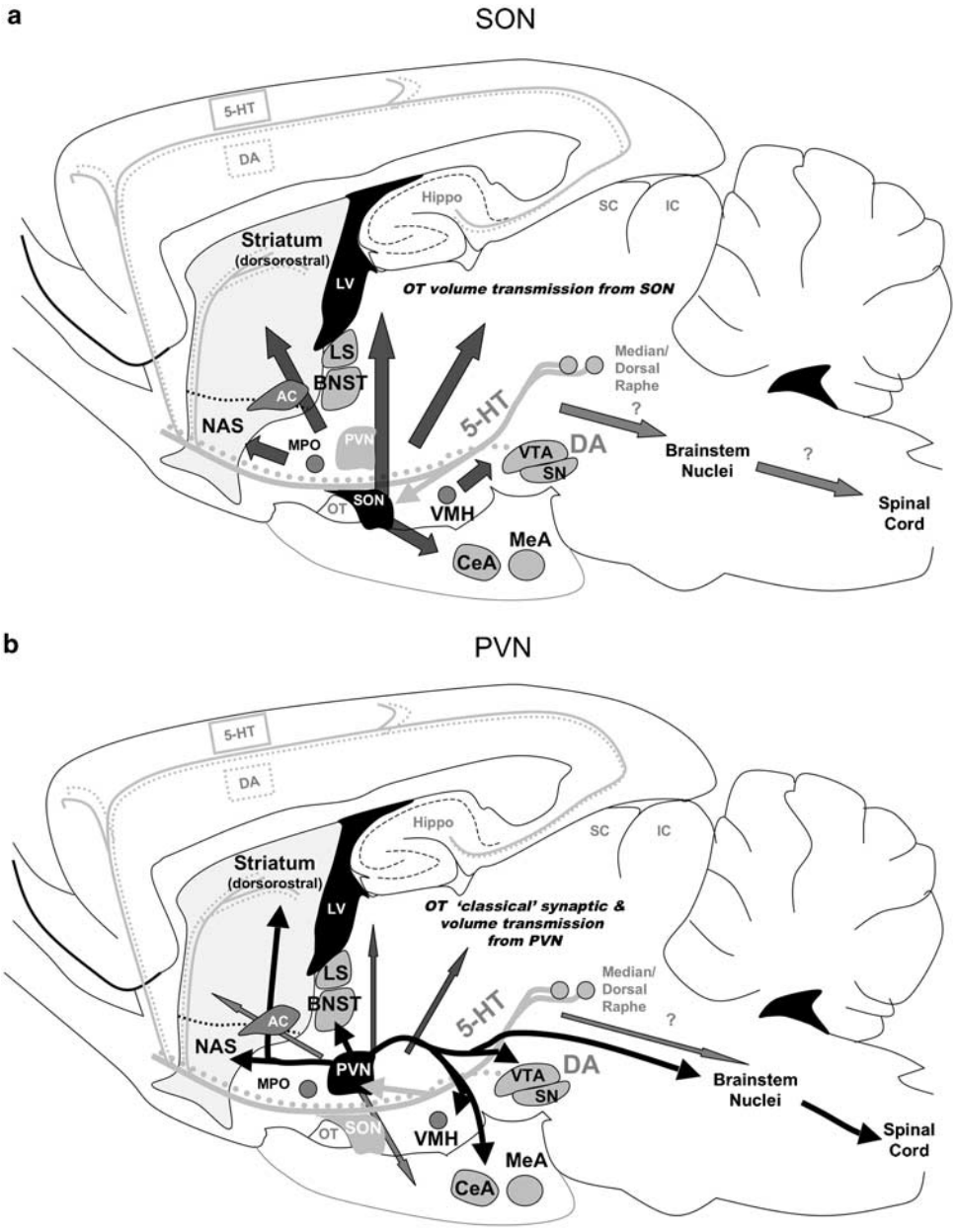

Figure 1 Schematic showing the possible interaction between central oxytocin release and addiction-relevant brain regions. (**a**) depicts dendritic release of oxytocin from the SON and its interaction with distal oxytocin receptor containing brain regions (volume transmission). (**b**) indicates both dendritic release of oxytocin from magnocellular PVN neurons and/or classical neurotransmission from PVN parvocellular oxytocinergic projections to forebrain, midbrain and spinal regions. Prosocial drugs (that is MDMA) release 5-HT via raphefugal fibres within PVN and SON and cause oxytocin release while oxytocinergic projections from the PVN to the VTA and NAS may modulate mesolimbic dopamine activity. PVN, paraventricular hypothalamic nucleus; SON, supraoptic hypothalamic nucleus; NAS, nucleus accumbens; LS, lateral septum; BNST, bed nucleus of the stria terminalis; MPO, medial preoptic area; VMH, ventromedial hypothalamus; CeA, central amygdaloid nucleus; MeA, medial amygdaloid nucleus; VTA, ventral tegmental area; SN, substantia nigra pars compacta; brainstem nuclei; spinal cord. AC, anterior commissure; OT, olfactory tract, SC, superior colliculus, IC, inferior colliculus; Hippo, hippocampus; DA, dopamine; CSF, cerebrospinal fluid.

the present article is according to Alexander *et al.*, 2007) elicits anxiolytic, antidepressant and prosocial effects (Griebel *et al.*, 2002; Stemmelin *et al.*, 2005; Shimazaki *et al.*, 2006). Indeed, OT and AVP circuits appear to have reciprocally inhibitory connections in regions such as the amygdala such that boosting OT 'shuts down' AVP circuitry and vice versa (Huber *et al.*, 2005). However, the situation is rather complex given that vasopressin V_{1a} receptors may have a prosocial role, with V_{1a} knockout mice showing social interaction deficits (Egashira *et al.*, 2007) and overexpression of V_{1a} receptors in regions such as the ventral pallidum linked to enhanced social bonding and mating-induced neural activation (Lim and Young, 2004). Arginine vasopressin is of great potential relevance to a range of behaviours relevant to addiction: for example a very recent report suggests that V_{1b} antagonists may prevent stress and

prime-induced heroin seeking in rats via an action on the amygdala (Zhou *et al*., 2008).

Oxytocin involvement in acute drug effects: MDMA as an example

The involvement of OT in the effects of abused drugs is a relatively under-researched area. Early findings, reviewed a decade ago (Kovacs *et al*., 1998), indicated that OT administration can influence opiate self-administration, cocaine-induced sensitization and the development of tolerance to opiates, cocaine and alcohol. Summarizing these early experiments, Kovacs *et al.* (1998) speculated that OT exerts a potent effect in inhibiting key neuroadaptations in mesolimbic, basal forebrain and hippocampal sites that may underlie addiction and tolerance to a wide range of drugs.

However, OT may also mediate some aspects of acute drug reward and intoxication. Systemically delivered OT is rewarding in rats, as shown in the place preference paradigm (Liberzon *et al*., 1997) and our own research has recently highlighted a role for OT in the acute effects of the popular dance party drug MDMA. At low doses, MDMA has a powerful 'prosocial' effect in rats, increasing social interaction in pairs of rats meeting for the first time (Morley and McGregor, 2000; Thompson *et al*., 2007). This effect is primarily due to an increase in a behaviour termed 'adjacent lying' (Figures 2a and b). MDMA causes hyperactivity in individually tested rats, so adjacent lying is not due to motoric impairment. Neither is it a 'huddling' response to perceived cold, as high ambient temperatures augment MDMA-induced adjacent lying and associated neural effects (Cornish *et al*., 2003; Hargreaves *et al*., 2007). Rather the effect may well model the powerful prosocial action of MDMA in humans (Dumont and Verkes, 2006; Sumnall *et al*., 2006).

These effects appear to involve the hypothalamic release of OT. Low, human-like, doses of MDMA activate OT-containing neurons in the SON and PVN of the hypothalamus (Figure 2c) and increase plasma OT levels in rats (Thompson *et al*., 2007). This interaction reflects the close proximity and confluence of 5-HT containing terminals and OT-containing cell bodies within the PVN and SON (Emiliano *et al*., 2006). In agreement with the findings from rats, raised peripheral OT is also seen in human MDMA users tested at a dance party (Wolff *et al*., 2006). Importantly, central administration of the OT receptor antagonist tocinoic acid (TOC, 20μg ICV), attenuates the prosocial effects of MDMA in rats, while not affecting baseline social behaviour (Figure 2b). High ambient temperatures increase brain OT release (Uvnas-Moberg *et al*., 1993) and this may explain our findings that high ambient temperatures potentiate the social, neural and rewarding effects of MDMA (Cornish *et al*., 2003; Hargreaves *et al*., 2007) and the tendency for human users to take MDMA under hot and sweaty conditions (Parrott, 2004).

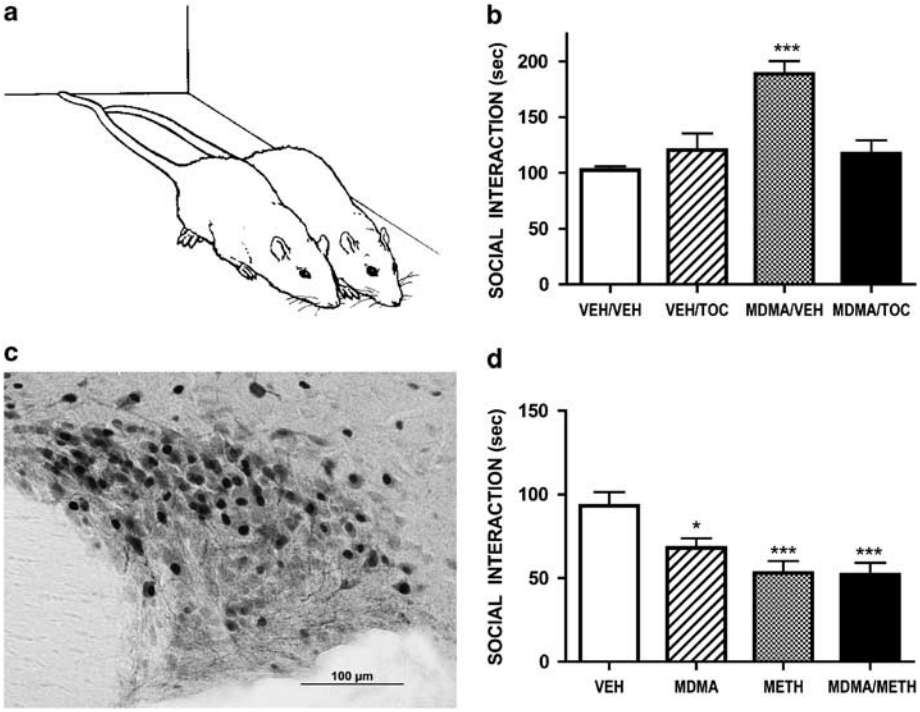

Figure 2 (**a**) Sketch of typical OT-mediated 'adjacent lying' behaviour seen in pairs of rats given low doses of MDMA. (**b**) The facilitation of social interaction produced by acute MDMA (5 mg kg^{-1}, i.p.) is reversed by intracerebroventricular administration of the OT receptor antagonist tocinoic acid (TOC, 20 μg). When administered alone tocinoic acid did not affect social interaction. Redrawn from Thompson *et al*., 2007. (**c**) Picture of the supraoptic nucleus of the hypothalamus showing staining for OT (brown) and Fos (black). MDMA (10 mg kg^{-1} significantly increases the number of double-labelled (oxytocin + Fos) neurons (see Thompson *et al*., 2007) (**d**) Administration of MDMA (8 mg kg^{-1}, i.p.), methamphetamine (METH, 8 mg kg^{-1}, i.p.) or the combination of MDMA (4 mg kg^{-1}, i.p.) + METH (4 mg kg^{-1}, i.p.) once per week for 16 weeks to rats causes a long-term decline in baseline social interaction measured 7 weeks after the last drug dose was administered. Redrawn from data presented by Clemens *et al*., 2007. *$P<0.05$, ***$P<0.001$.

The prosocial effects of MDMA are mimicked by the 5-HT_{1A} receptor agonist 8-OH-DPAT, which is also a potent releaser of OT. Moreover the 5-HT_{1A} antagonist WAY 100 635 blocks both MDMA-induced OT release and prosocial effects (Thompson *et al*., 2007; Thompson *et al*., 2008). These results give a preliminary indication that the functional social effects of MDMA, which are a key reason for the widespread use of the drug, depend upon 5-HT_{1A}-mediated OT release. Tolerance to this effect with repeated MDMA exposure may underlie the loss of sensitivity to the positive effects of MDMA in heavy users, and may result in the dose escalation commonly seen in MDMA users over time (Thompson *et al*., 2008).

While MDMA provides a strong *prima facie* case for OT involvement in positive drug effects, evidence for other OT involvement in the effects of other commonly used drugs is rather scarce. The other popular dance party drug GHB is similarly prosocial to MDMA, has anti-aggressive and anxiolytic properties (Schmidt-Mutter *et al*., 1998; Pedraza *et al*., 2007; Sumnall *et al*., 2008), and causes powerful activation of SON oxytocinergic neurons (Van Nieuwenhuijzen *et al*., unpublished data). Indeed, GHB was once used to promote uterine contractions in childbirth, suggestive of a powerful OT-stimulating effect (Geldenhuys *et al*., 1968). Low doses of nicotine also powerfully activate SON neurons via cholinergic innervation of this structure (Matta *et al*., 1993) and SON and PVN neurons show profound alterations in firing rate during the development of opiate tolerance and withdrawal (Brown and Russell, 2004). Acute cocaine produces a dose-dependent increase in hypothalamic and hippocampal OT release (Kovacs *et al*., 1998). Further circumstantial evidence suggestive of a role for OT in the incentive motivational properties of drugs comes from considering the interaction between OT and brain dopamine pathways.

Oxytocin interaction with the mesolimbic dopamine system

The mesolimbic dopamine system, connecting the midbrain ventral tegmental area (VTA) with the nucleus accumbens (NAS) and other forebrain structures, plays a long-celebrated and much discussed role in the incentive motivational processes underlying the response to natural rewarding stimuli, addictive drugs and drug-related cues. A critical interaction between OT and this brain module is evident from several elegant studies of rodent sexual and social behaviour.

OT-containing neurons in the PVN promote penile erection and copulatory behaviour via their central and spinal projections (Melis and Argiolas, 2003). Oxytocinergic projections from the PVN to the VTA innervate the dopaminergic neurons that project to the nucleus accumbens and this circuit has a prosexual effect: OT infused into the caudal VTA or PVN causing penile erections, increased sexual motivation and increased mesolimbic dopamine activity (Melis *et al*., 2007). OT is also released during ejaculation, an event that is associated with VTA activation in human subjects (Holstege *et al*., 2003) and a recent case report suggests the utility of intranasal OT for male anorgasmia (Ishak *et al*., 2008). OT also appears responsible for the reduced anxiety that is typical of the post-orgasmic state (Waldherr and Neumann, 2007). To the extent that drugs of abuse 'piggyback' upon or 'hijack' natural reward circuits (Kauer and Malenka, 2007), we have an interesting liaison between the substrates of sexual reward and drug reward that may involve OT. The prosexual effects of drugs such as GHB, cocaine and methamphetamine might conceivably have an OT component.

Sexual intercourse in monogamous species gives rise to lasting pair bonds with compelling evidence that OT acting within the dopaminergic circuitry of the nucleus accumbens facilitates this process (Lim and Young, 2006). The enduring partner preference that is produced by sexual intercourse in monogamous prairie voles is blocked by both dopamine antagonists or OT antagonists injected into the NAS (Aragona *et al*., 2006; Lim and Young, 2006). Thus OT, acting in concert with dopamine D_2 receptors in the NAS, serves to imbue a particular conspecific with special significance. This has lead to the speculations that social attachment may be some form of addictive disorder (Insel, 2003) and that the same OT circuitry that mediates addiction to love in monogamous species may well mediate addiction to drugs (Edwards and Self, 2006). At present, these remain fascinating ideas in search of confirmatory data.

The mesolimbic and ventral pallidal processes involving OT and AVP that allow social bonding between two mammals may also serve to generate social exclusion, so that the opportunity to bond with other prospective partners is subsequently rejected once a monoaganous bond is formed (Aragona *et al*., 2006; Lim and Young, 2006). This process appears to involve a proliferation of D_1 receptors in the rostral shell of the NAS. One is reminded here of the exclusivity with which addicts bond to their drugs, with the pathological salience of drug-related cues relegating family, friends and natural rewards to a peripheral role in the addict's life (Robinson and Berridge, 1993). It is notable here that exclusivity of bonding is also manifest in maternal behaviour, with OT appearing to subserve an important role not only in maternal 'calmness' but in the protective aggression seen in new mothers (Slattery and Neumann, 2008).

Clearly much work remains to be done to confirm exactly how, and to what extent, OT impinges upon mesolimbic dopamine activity to influence the acute reinforcing actions of drugs and the neuroplasticity in this and related regions (VTA, dorsal striatum, prefrontal cortex and amygdala) that underlies compulsive drug seeking. The ability of OT to attenuate the repetitive, stereotyped behaviours that are characteristic of autism (Hollander *et al*., 2003), stimulant-induced hyperactivity (Qi *et al*., 2008) and drug-induced sensitization (Kovacs *et al*., 1998) suggests that although OT may contribute towards the acute reinforcing properties of drugs it may also serve to put a 'brake' on their more excessive long-term, habit-promoting effects. Interestingly, a 'brake-like' effect of OT is also evident from studies of palatable fluid consumption where OT knockout mice are found to consume greater amounts of saccharin, sucrose and nonsweet carbohydrate (cornstarch, polycose) solutions

than wild types (Amico *et al*., 2005; Billings *et al*., 2006; Sclafani *et al*., 2007). While this may simply reflect a general role of hypothalamic OT in the regulation of appetite and fluid balance (Verty *et al*., 2004) it may speaks of a more specific role of the neuropeptide in promoting satiety, a role that could be relevant to the termination of drug and as well as food intake.

Oxytocin amelioration of drug withdrawal effects

Some intriguing evidence speaks about the ability of OT to ameliorate physical and behavioural effects associated with drug withdrawal. To the extent that drug withdrawal represents an aversive, anxiogenic and agitated state it is perhaps not surprising that this neuropeptide with anxiolytic, serenic and anti-stress properties should be potentially therapeutic in this situation (see Table 1).

In a key study, withdrawal symptoms arising from sudden precipitated cannabinoid abstinence in rats and were reversed by administration of lithium, via an OT-dependent mechanism (Cui *et al*., 2001). Lithium produces pronounced activation of OT-positive hypothalamic nuclei and the ability of lithium to prevent abstinence effects was reversed by co-administration of the OT antagonist L-368,899. Moreover, L-368,899 given in the absence of lithium, exacerbated the cannabinoid withdrawal syndrome. 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). These findings have prompted preliminary trials of lithium in treating cannabis withdrawal with encouraging results (Bowen *et al*., 2005; Winstock *et al*., in press) and such trials could conceivably be extended to future examination of intranasal OT or other OT-releasing compounds as therapeutics.

The neural mechanics underlying such effects are worthy of some speculation. Withdrawal from many drugs of abuse, including ethanol, cannabinoids, nicotine and opioids is associated with increased release of corticotropin releasing factor (CRF) in the amygdala. Accordingly, CRF antagonists have a potent and well-documented effect in blocking withdrawal-induced anxiety and drug-seeking behaviour in rodent models (Rodriguez de Fonseca *et al*., 1997; George *et al*., 2007; Heilig and Koob, 2007). It is therefore interesting to note that OT has marked inhibitory effects on activation of the hypothalamic pituitary adrenal axis (Uvnas-Moberg, 1998; Legros, 2001; Windle *et al*., 2004) and centrally administered OT, but not AVP, exerts a potent action in suppressing stress-induced Fos expression in sites such as the hypothalamus and hippocampus (Windle *et al*., 2004). It would therefore appear timely to explore the action of OT in animal models that explore the influence of stress on drug seeking behaviour, such as the reinstatement paradigm. The capacity of OT to antagonize AVP effects in the amygdala (Huber *et al*., 2005), and the demonstrated role of amygdala AVP in drug-seeking (Zhou *et al*., 2008), invites the suggestion that OT might inoculate against stress-induced relapse to drug seeking.

Incidentally, a recent theoretical analysis of autism (Schulkin, 2007) sees the interplay between CRF and OT in the central and medial amygdala as a fundamental determinant of social approach and avoidance. Dominance of CRF over OT is hypothesized to cause profound social withdrawal and an anxious, stress-sensitive and novelty-averse state typical of autism and perhaps drug withdrawal. Recent clinical studies of OT as a therapeutic for autism have lead to some encouraging results (Hollander *et al*., 2003, 2007).

Residual social deficits caused by drug exposure

While MDMA exerts an acute prosocial effect on rats (Figure 2a), we and others have repeatedly noted that rats given even brief exposure to small doses of MDMA show subsequent deficits in social interaction, effects that can be detected many weeks and months after drug exposure (Figure 2d, Table 2). Thus the short-term 'ultrasocial' state produced by MDMA appears to be followed by a much longer lasting 'antisocial' state. The behavioural changes occurring as a result of MDMA pre-exposure are not only social in nature: pre-exposed rats show prolonged increases in anxiety on the elevated plus maze and emergence tests, have poorer memory than controls and are impaired in their coping responses to acute stress in the forced swim test (Morley *et al*., 2001; McGregor *et al*., 2003b; Thompson *et al*., 2004).

Table 1 Schema of general psychological effects of brain oxytocin and those associated with acute drug intoxication, addiction and withdrawal

Effect	*Oxytocin*	*Intoxicated*[a]	*Addicted*	*Withdrawal*
Sociability	↑	↑	↓	↓
Trust	↑	↑	↓	↓
Mood	↑	↑	↓	↓
Coping with stress	↑	↑	↓	↓
Aggression/irritation	↓	↓↑	↑	↑
Stereotyped behaviours	↓	?	↑	?
Drug craving	?	↓ ↑	↑	↑
Anxiety	↓	↓	↑	↑

See text for relevant references.
↑ Increase, ↓ Decrease, ? Effects unclear.
[a]It is acknowledged that these acute effects may vary from one drug to another.

Table 2 Lasting social interaction deficits in rodents following drug exposure

Drug	*Example references*
MDMA (Ecstasy)	Bull *et al*., 2003; Clemens *et al*., 2004, 2007; Fone *et al*., 2002; Morley *et al*., 2001; Morley *et al*., 2004; Thompson *et al*., 2004
Methamphetamine	Clemens *et al*., 2004, 2007
Cannabinoids	O'Shea *et al*., 2004, 2006; Quinn *et al*., 2008
Phencyclidine	Boulay *et al*. 2004; Sams-Dodd, 1996; Snigdha and Neill, 2008
Ketamine	Becker and Grecksch, 2004; Koros *et al*., 2007
Opiates	Blatchford *et al*. (2005)
GHB	Van Nieuwenhuijzen *et al*. (2007)

These effects are mirrored in some recent studies of human MDMA users, where anxiety and depressive disorders may be over-represented and impairment in processing of social cues is evident (Parrott and Marsden, 2006; Reay *et al*., 2006).

MDMA is not the only drug that leads to lasting social interaction deficits in animal models. Our group, and others, have reported similar lasting social deficits in rats given brief exposure to methamphetamine, cannabinoids and NMDA antagonists such as ketamine and phencyclidine (Table 2). Indeed, the social withdrawal caused by subchronic exposure to NMDA antagonists is an increasingly popular animal model of negative symptomatology in schizophrenia. Importantly, the social withdrawal caused by repeated exposure to PCP is reversed by intra-amygdala administration of OT (Lee *et al*., 2005) suggesting that long-term adaptations in brain OT systems plays a critical role in the effect. Vasopressin V_{1a} agonists can also have a beneficial effect in restoring social behaviour after exposure to NMDA antagonists (Matsuoka *et al*., 2005).

If drug abuse were causing lasting neuroadaptations in brain OT systems then major deficits in maternal behaviour would also be predicted as a result of drug exposure (Jin *et al*., 2007). In humans, child neglect appears to be both a cause and consequence of drug abuse and there is evidence that such effects may involve OT (Carter, 2005). Consonant with this, various studies have documented OT-related deficits in mothering in rodents following exposure to methamphetamine or cocaine, including reduced pup-directed behaviours, impaired nest building and overly aggressive maternal defence (Johns *et al*., 2005; Slamberova *et al*., 2005; Jarrett *et al*., 2006). Moreover, *in utero* exposure to drugs of abuse such as cocaine cause lasting changes in the brain OT system of offspring (Johns *et al*., 2005; Jarrett *et al*., 2006), and this could conceivably lead to lasting adverse effects on their social behaviour into childhood and beyond (Tronick *et al*., 2005; Barr *et al*., 2006). It is tempting to speculate that the high prevalence of early trauma and abuse reported in adults with drug use disorders (Reed *et al*., 2007) may reflect a vulnerability that arises from abnormal development of brain OT systems.

Oxytocin-related neuroadaptations: lasting adverse effect of drug use?

Lasting social dysfunction as a result of drug exposure is thus evident in studies with laboratory animals (Table 2), although the neuroadaptations that mediate such effects are not well defined. While MDMA has well-documented effects in depleting brain 5-HT, this does not appear to be the key factor causing lasting social changes, since these occur with low or intermittent doses of MDMA that do not affect 5-HT (McGregor *et al*., 2003a; Clemens *et al*., 2007) and are seen with exposure of other drugs of abuse that do not greatly influence 5-HT systems (Table 2). Rather, it appears that some other major neuroadaptation is occurring, and it is therefore interesting to turn our attention to brain OT.

The OT systems of the brain 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 (Gimpl and Fahrenholz, 2001; Kramer *et al*., 2006; Neumann, 2007; Slattery and Neumann, 2008). With respect to drugs of abuse, repeated administration of low-dose THC caused downregulation of OT receptor expression and diminished OT innervation in the nucleus accumbens of rats (Butovsky *et al*., 2006). It is notable here that cannabinoids are known to cause lasting social deficits in rats (O'Shea *et al*., 2004, 2006; Quinn *et al*., 2008). In other relevant studies, chronic morphine exposure was found to decrease brain OT synthesis (You *et al*., 2000), chronic ethanol exposure was associated with degeneration of OT containing magnocellular neurons in the hypothalamus of both humans and rats (Silva *et al*., 2002; Sivukhina *et al*., 2006) and repeated cocaine administration caused a decline in hippocampal and hypothalamic OT levels (Kovacs *et al*., 1998). More recent, albeit preliminary, findings suggest that both MDMA and GHB can cause lasting alterations in OT and OT receptor gene expression in rats that are associated with the social interaction deficits described above (Van Nieuwenhuijzen *et al*., 2007). Brain-wide assessment of altered OT and OT receptor levels and associated gene expression after repeated drug exposure would clearly be a worthy pursuit for future studies.

Conclusions and future directions

The evidence reviewed here suggests that OT may act as a key component of the rewarding prosocial effects of certain drugs, may have a strong capacity to influence addiction-relevant neuroadaptations, may ameliorate anxiety and irritability during drug withdrawal and that drug-induced disturbances in brain OT may underlie the adverse social consequences arising from repeated drug exposure. On the other hand, it has also long been known that psychosocial support can be a vital component in allowing recovery for addictions and one wonders whether OT might play a role as a natural substrate for such therapeutic effects (see for example, Grewen *et al*., 2005). In addition, to the extent that addicts are caught in something of a behavioural loop, it is interesting to note the ability of OT to attenuate highly repetitive and compulsive stereotyped behaviours (Hollander *et al*., 2003). Clearly, an improved characterization of OT and related neuropeptide involvement in a range of acute drug actions and addiction-related neuroadaptations is a timely endeavour that may yield major dividends.

Most interesting perhaps is the possibility that drugs targeting central OT receptors may provide a novel pharmacotherapy for treatment of drug withdrawal and drug craving. A major problem here is that systemically delivered OT has very poor penetration of the CNS, with nasal delivery being the only successful current CNS delivery system in human studies. Even then, there is still uncertainty as to how well intranasal OT penetrates the brain and the longevity of its action (Born *et al*., 2002). Development of novel OT agonists is at an early stage and faces considerable technical hurdles (Chini and Manning, 2007). Nonetheless, even with the current limited range of tools available, there is considerable scope to further examine the role of OT in the

acute effects of popular recreational drugs and the capacity of this 'social neuropeptide' to reverse the anxiety, depression and social disconnection experienced by many who battle drug addiction.

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Conflict of interest

The authors state no conflict of interest.

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