A brief history of oxytocin and its role in modulating psychostimulant effects
Dean S Carson, Adam J Guastella, Emily R Taylor and Iain S McGregor
J Psychopharmacol published online 23 January 2013
DOI: 10.1177/0269881112473788

The online version of this article can be found at:
http://jop.sagepub.com/content/early/2013/01/14/0269881112473788

Published by:
SAGE
http://www.sagepublications.com

On behalf of:
British Association for Psychopharmacology

Additional services and information for Journal of Psychopharmacology can be found at:

Email Alerts: http://jop.sagepub.com/cgi/alerts
Subscriptions: http://jop.sagepub.com/subscriptions
Reprints: http://www.sagepub.com/journalsReprints.nav
Permissions: http://www.sagepub.com/journalsPermissions.nav

>> OnlineFirst Version of Record - Jan 23, 2013

What is This?
Introduction

A historical overview of oxytocin

Oxytocin (OT) is a nine-amino acid cyclic neuropeptide produced in the paraventricular nucleus (PVN) and supraoptic nucleus (SON) of the mammalian hypothalamus. It is released into peripheral circulation via the posterior lobe of the pituitary gland (i.e. the neurohypophysial system) and widely throughout the brain according to varying mechanisms. OT acts to influence an immense number of complex central and peripheral physiological functions. The contemporary Greek name for OT is “ωκυτοκίνη” (pronounced as okitokini), which is derived from the ancient Greek words ωκύς and τοκετός meaning “quick birth”. As this name suggests, OT is best known for its role in parturition during which it facilitates uterine contractions.

In 1906, the renowned British physiologist Sir Henry H Dale discovered that extracts from the posterior portion of oxen pituitary glands facilitated uterine contractions when administered intravenously (i.v.) to cats, dogs, guinea-pigs, rabbits, and rats (Dale, 1906, 1909). The initial report of these findings can be found embedded in a 1906 research paper outlining the general physiological action of the rye fungus ergot that Dale published whilst working at the Wellcome Laboratory in London (Dale, 1906). In 1909, the clinical potential of Dale’s seminal findings on OT was realized by the celebrated British obstetrician and gynecologist William Blair Bell. Bell claimed that infundibulin (originally sold by Burroughs Wellcome & Company) not only rapidly facilitated uterine contractions to assist in fetal delivery, but also prevented postpartum hemorrhage, and provided considerable relief for male and female patients suffering from severe constipation (see (Bell, 1909) for a detailed discussion of these effects). Following Dale and Bell’s initial discoveries for the role of OT in parturition, the ability of infundibulin to stimulate milk ejection was also outlined in animals (Ott and Scott, 1910; Schafer and Mackenzie, 1911) and shortly after in humans (Mackenzie, 1911; Schafer, 1913).
Until the late 1930s, it was assumed that the site of formation of hormones found in the neurohypophysis were the pituicytes of the infundibular process (Gersh, 1939). Ernst and Berta Scharrer (Scharrer and Scharrer, 1937) provided the first evidence that neurons of the SON and PVN passed along axonal projections to the infundibular process. Due to the technical limitations of the time, these findings were not fully realized until Bargmann (1949), using Gomori’s (1939) chrome-hematoxylin staining technique, outlined evidence that axons projecting from the SON and PVN of the hypothalamus were indeed responsible for transporting material from these nuclei to the neurohypophysis. Bargmann referred to the projection of hypothalamic fibers to the neurohypophysis as the “neurosecretory pathway”. These original discoveries were published in German, but see Bargmann and Scharrer (1951) for an English language discussion of these and other interesting findings. Also see reviews by Klavdiviev (1996) and Engelmann et al. (2004).

In the early 1950s, American biochemist Vincent du Vigneaud identified the nine-amino acid sequence of OT (du Vigneaud et al., 1953) (see Figure 1). Through comparative analysis of the toco- genic and mammory gland stimulatory effects of several synthetic compounds with naturally derived OT, du Vigneaud synthesized this polypeptide hormone for the first time (du Vigneaud, 1955; du Vigneaud et al., 1954). These findings further strengthened earlier claims that OT could be used clinically to stimulate uterine contractions and milk let-down reflex as it allowed for the administration of pure synthetic OT solutions to human subjects (Bosch and Kaser, 1956; Francis and Francis, 1956; Nickerson et al., 1954). This work represented the first characterization and synthesis of a neuropeptide and resulted in a Nobel Prize in Chemistry for du Vigneaud in 1955. It is interesting to cite an optimistic statement made by Bell: “[There is] a definite promise that in the near future the chemist will be able to synthesize the active principle of the infundibular body” (1909: 1613). This statement was made almost 50 years prior to du Vigneaud’s discovery, further highlighting the importance of his work.

Since these initial discoveries, OT has become one of the most highly researched neuropeptides in the mammalian nervous system. It has played a major role as a therapeutic tool in clinical obstetrics thanks to its widespread use in the induction of labor (Alfirevic et al., 2009) and has become the treatment of choice for managing postpartum hemorrhage (Su et al., 2007). Many physicians also continue to prescribe OT for facilitating the milk let-down reflex in patients suffering from severe mastitis; however, the evidence for its efficacy in this indication is debated (Fewtrell et al., 2006; Ruis et al., 1981). Other research now suggests OT has broad involvement in many other peripheral and central physiological processes including the regulation of water balance and blood osmolality (Li et al., 2008), cardiac function (Alizadeh et al., 2010), bone density (Tamma et al., 2009), appetite and fat metabolism (Deblon et al., 2011; Eckertova et al., 2011), and in the modulation of social behavior (e.g. pair bonding and parental care) (Donaldson and Young, 2008) and cognition (e.g. learning and memory) (Engelmann et al., 1996).

Pioneering research conducted throughout the 1980s and 1990s by Hungarian researchers suggested a role for OT in modulating both the neuronal and behavioral processes associated with alcohol, cocaine, and opiate administration in rodents (see Kovacs et al., 1998; Sarnyai, 1998; Sarnyai and Kovacs, 1994 for thorough reviews of this work). This work emerged out of early observations that opiates and alcohol, administered as analgesics during childbirth, acted to inhibit the stimulatory effects of OT on uterine contractions and milk-ejection (Cobo, 1973; Fuchs and Wagner, 1963; Lutz-Bucher and Koch, 1980). Although the early research into OT’s modulatory role on psychoactive drug effects was elegantly conducted and ground breaking in its results, it has taken more than a decade for it to be adequately extended. The current climate of neuroscientific and psychological/psychiatric research has created an atmosphere in which we now see a deluge of preclinical and clinical research on OT, with new findings pointing towards the clinical application of this neuropeptide in a wide variety of psychiatric disorders, including drug addiction. Following a brief overview of basic OT physiology we will discuss some of the pharmacological complexities in this field and outline key findings supporting OT’s broad action on brain and behavior. Finally, we will provide a thorough review of the modulatory role of OT with regard to psychostimulant effects with a particular focus on amphetamine-type stimulants (i.e. methamphetamine (METH) and 3,4-methylenedioxymethamphetamine (MDMA, Ecstasy)).

**Important aspects of OT physiology**

**Oxytocin release sites and receptor distribution**

In 1984, the OT gene was cloned, allowing mapping of the distribution of OT mRNA throughout the mammalian nervous system (Ivell and Richter, 1984). Although it is synthesized in peripheral tissues such as the uterus, placenta, amnion, corpus luteum, testis, and the heart the major site of OT gene expression is the magnocellular (large) neurons of the hypothalamic PVN and SON, whose axonal projections converge on the posterior pituitary for release into peripheral circulation (Gimpl and Fahrenholz, 2001; Sofroniew, 1983; Viero et al., 2010). OT is also produced in the paraventricular (small) neurons of the PVN and released into peripheral circulation from axon terminals that converge on the blood–brain barrier (BBB) free area of the median eminence (Antoni, 1993; Engelmann et al., 2004; Rodriguez et al., 2010).

Importantly, OT is released from dendrites and somata (cell bodies) in the PVN and SON, where it is considered to impact on a broad network of extrahypothalamic brain regions via volume transmission (see Landgraf and Neumann, 2004 for an extensive review). Depending on the species, evidence suggests that OT is also present in brain regions such as the bed nucleus of the stria terminalis (BNST), medial preoptic area (MPOA), and lateral amygdala (LA) (Young and Gainer, 2003). There is continued debate, however, as to whether OT released in these extrahypothalamic brain regions results from the dendrites/somata of unidentified OT cell bodies or from axonal projections/volume transmission from OT-containing neurons in the PVN (Landgraf and Neumann, 2004; Neumann, 2007). There is some evidence that scattered OT fibers projecting from magnocellular hypothalamic neurons lie in

---

**Figure 1.** Nine amino acid sequence of the oxytocin molecule. The bridge between the two cysteine amino acids represents a disulfide bond. H: hydrogen; Cys: cysteine; Tyr: tyrosine; Ile: isoleucine; Gln: glutamine; Asp: aspartagine; Pro: proline; Leu: leucine; Gly: glycine; NH2: amine
diverse brain regions including, but not limited to, the hippocampus, cortex, amygdala, substantia nigra (SN), ventral tegmental area (VTA), raphe nucleus, parabrachial nucleus, locus coeruleus, and densely throughout the brain stem and spinal cord; areas important in a broad range of complex psychological and physiological processes (Sofroniew, 1980, 1983; Sofroniew et al., 1981).

In 1992, the structure and expression pattern of the sole OT receptor (OTR) was elucidated in human myometrium cells (Kimura et al., 1992). The OTR is a 389 amino acid polypeptide with seven transmembrane domains that belongs to the class I G protein-coupled receptor family. These receptors are expressed in diverse peripheral anatomical regions such as the uterus, mammary gland, ovary, kidney, heart, bone, and endothelial cells (see Gimpl and Fahrenholz, 2001 for review). Additionally, OTRs are widely distributed throughout the mammalian central nervous system (CNS). Specifically, in the rat brain, OTRs are found in areas such as the olfactory bulb and tubercle, neocortex, endopiriform cortex, hippocampus, central amygdala (CeA), LA, BNST, nucleus accumbens (NAcc), and ventromedial hypothalamus (VMH) (Vaccari et al., 1998; Yoshimura et al., 1993). The role of these brain areas in various psychiatric disorders, including addiction, and the effects that OT exerts on their function will be discussed later in the paper.

**Neuroplasticity in the oxytocinergic system**

OT released from the somata and dendrites of magnocellular neurons in the PVN and SON, in addition to acting on extrahypothalamic brain regions, has been shown to stimulate further OT release by binding back onto the OT receptors found on these same neurons. This “self-stimulating” action results in a positive-feedback loop (Moos et al., 1984) (see Landgraf and Neumann, 2004 for review). In fact, OT is considered the model peptide for the positive-feedback loop, and its self-stimulating action helps to explain its effects on uterine contractions and milk let-down. During labor, initial uterine contractions provide a signal for OT to be released from neurons in the hypotalamus, which are upregulated in the PVN and SON during late pregnancy. OT then binds to and stimulates OTRs in both the myometrium and hypotalamus, which are also upregulated during late pregnancy. This activity results further in uterine contractions and greater release of hypotalamic OT (Armstrong and Hatton, 2006; Kimura et al., 2003; Neumann et al., 1996). This release pattern occurs in a pulsatile manner, allowing for smooth muscle tissue to recover vital energy stores before being called upon to provide further uterine contractions until delivery is complete (Armstrong and Hatton, 2006). The feed-forward function of OT, during parturition, is commonly referred to in obstetrics as the “Ferguson reflex” (Ferguson, 1941).

One of the most intriguing aspects of the OT system is that it is exceptionally dynamic and plastic, and is highly open to rapid morphological change. Theodosis and colleagues (2006) provide an enlightening review detailing the extensive changes that the OT system undergoes during a diverse range of physiological conditions. In the SON, OT neurons are often found in tightly packed clusters separated by fine processes of astrocytes (glia). During stimulated conditions such as parturition or lactation, OT neurons are contacted by an increased number of synapses and the glial coverage of the OT neurons is significantly reduced, allowing for the neurons to shift position so that the dendrites and somata of OT neurons are juxtaposed. This reorganization allows for enhanced OT communication between neurons and facilitates the quantity of OT released into the periphery for promotion of important physiological functions such as uterine contractions and milk let-down. When OT secretion returns to baseline and is no longer required for facilitating the physiological process (e.g. following childbirth or weaning of the young) the glial ensheathment of OT neurons is once more established and OT neurons are reorganized so they are no longer juxtaposed (Theodosis et al., 2006).

This plasticity is especially important when considering not only adaptive physiological and environmental conditions (e.g. pair bonding, parental care, and reproduction) but also maladaptive conditions (e.g. chronic stress, social isolation, and substance abuse) (McGregor and Bowen, 2012; McGregor et al., 2008). The detrimental effects of psychostimulant drugs on the OTergic system will be discussed in more detail later in this review.

**Pharmacological considerations**

**Drug development and exogenous OT administration**

Commercially available peptide-like OT agonists and antagonists for use in obstetrics include *Pitocin* (synthetic OT for i.v. and intramuscular (i.m.) administration; King Pharmaceuticals), *Syntocinon* (synthetic OT for i.v., i.m., and intranasal administration; Novartis), *Duratocin* (carbetocin) a long acting OT analogue for i.v. and i.m. administration; Ferring Pharmaceuticals), and *Tractocile* (atosiban) synthetic OT antagonist for i.v. administration; Ferring Pharmaceuticals). Although useful treatments in obstetrics, these drugs typically show limited specificity to OTRs due to significant affinity overlap with arginine vasopressin (AVP) receptors (V1a, V1b, V2). These two highly related nonapeptides and their receptors show significant sequence homology, often making it difficult to tease apart their specific action (Manning et al., 2008). Several academic and commercial laboratories have contributed substantially to the development of novel OTR ligands during recent years (Borthwick, 2010; Manning et al., 2008, 2012). Although this research has been relatively productive in developing small molecule non-peptide antagonists suitable for use in obstetrics and/or preclinical research, it has struggled to generate any convincing evidence for candidate drugs acting on central OTRs (Hicks et al., 2012; Ring et al., 2010). At present, synthetic forms of OT (especially *Syntocinon*) represent the best agonist treatments but also maintain several limitations.

Oral dosing with OT is not considered a viable administration route given that polypeptides undergo inactivation in the gastrointestinal tract and a significant first pass metabolism in the liver (Lee, 1988). Further, given the relatively large size of OT (1007 daltons), parenteral injections of OT are unlikely to reach the brain in significant quantities due to the restrictions of the BBB (Ermisch et al., 1985). Nasal routes of administration may overcome these problems for other polypeptides (AVP and insulin) but research has been slow in providing direct evidence for OT penetrating the brain via the intranasal route (Born et al., 2002; see Chang et al., 2012 for very preliminary data in monkeys). It is argued that nasal administration of large molecule drugs may bypass the BBB instead entering the CNS through the intracellular junctions of the olfactory epithelia (Balin et al., 1986; Zhu et al., 2012). It has also been suggested that high dose
i.v. injections of OT enter the brain in significant quantities via circumventricular organs that maintain “leaky” capillary endothelial junctions (e.g. the area postrema, subfornical organ, and organum vasculosum laminae terminalis). It is also possible that these high i.v. doses enter the brain in very small quantities (1–2%) via areas that maintain tight capillary endothelial junctions (Ermisch et al., 1985; Landgraf et al., 1979). However, high doses of i.v. OT are also associated with significant cardiovascular side-effects (hypotension, tachycardia, myocardial infarction) making this an unfavorable administration route for CNS stimulation in humans (Dyer et al., 2011).

Given the limitations outlined above, the development of small non-peptide OT agonists that maintain enhanced specificity to central OTRs is clearly desirable. Importantly, a large number of studies (see next sections) have consistently outlined the ability of intranasal OT to modulate a wide variety of complex behavioral and neural processes with minimal side-effects making this an attractive administration route for human studies. For an overview of the safety, side-effects, and subjective reactions to intranasal OT see a recent review by MacDonald et al. (2011). This study concluded that intranasal OT produces no detectable subjective changes in recipients and is associated with no reliable side-effects or adverse events when delivered in single doses of 18–40 IU (~1.68 µg/IU) for short term use in controlled research settings. MacDonald and colleagues also encouraged further research on intranasal OT with a focus on dosage and duration, and application with younger age groups inclusive of both male and female participants. Other research has provided evidence that intranasal OT, even when given in very high doses (up to 320 IU) and following a chronic dosing regimen (up to 13 weeks, b.i.d.), resulted in no serious adverse events and caused only minimal side-effects (Epperson et al., 1996; Feifel et al., 2010, 2012; Ohlsson et al., 2005; Pedersen et al., 2011).

Endogenous OT activity and limitations with its measurement

An increasing number of studies have aimed to outline the relationship between plasma and cerebrospinal fluid (CSF) levels of OT with complex psychological processes in both healthy and clinical populations (Green et al., 2001; Hammock et al., 2012; Heim et al., 2009; Lee et al., 2009; Modahl et al., 1998; Parker et al., 2012; Sasayama et al., 2012; Scantamburlo et al., 2007). An important factor to consider when interpreting this research is the relationship between central and peripheral OT activity. As outlined above, OT neurons have distinct projection sites from the hypothalamus to extrahypothalamic brain regions for central activity and the posterior pituitary and median eminence for release into peripheral circulation. Evidence suggests that central and peripheral OT can be independently regulated, meaning that plasma OT may provide a poor proxy for central OTRergic tone (Ludwig and Leng, 2006; Neumann et al., 1993). For example, Engellman and colleagues (1998) provided evidence that social defeat in rats stimulates the release of OT in the extracellular fluid of the SON but does not alter plasma OT concentration.

Under certain conditions, however, central and peripheral OT has been reported to act with some synchrony. For example, Wotjak et al. (1998) aimed to determine the relationship between central (PVN and SON) and peripheral OT in rats during the forced swim stress test. They showed that OT levels in the extracellular fluid of the SON and plasma were closely related. Despite this, spatial and temporal characteristics of OT central diffusion into extracellular fluid and CSF currently remain unclear meaning that measurement of OT in these substances might not yet be an accurate representation of central OT activity (Landgraf and Neumann, 2004). Further clarifying the relationship between central and peripheral OT will certainly enhance the quality of interpretation of research emerging from the behavioral sciences and may contribute to the use of plasma and/or CSF OT levels one day being used as a clinical biomarker for CNS disorders (Neumann and Landgraf, 2012).

There is also an ongoing debate about the quality of the technology used in assaying OT in biological samples. Significant variation in the levels reported by different research groups is dependent on the chosen measurement technique (radio- or enzyme immunoassay technology; peptide extraction or sample dilution) and the biological matrix being assayed (blood, CSF, saliva, urine) (Carter et al., 2007; Szeto et al., 2011). A recently published methods paper from Pfizer researchers outlined the use of a novel two-dimensional liquid chromatography-tandem mass spectrometry assay to measure OT in human and rat plasma (Zhang et al., 2011). This technique is reported to have an impressive lower limit of detection for human plasma of 1 pg/mL, but a less impressive 50 pg/mL for rats. Developments such as these are exceptionally important and should continue to be investigated as a matter of priority.

OT’s action on diverse behavioral processes

The role of OT in fear and avoidance behaviors

The efficient acquisition of avoidance behaviors towards threatening stimuli is an adaptive process necessary for ensuring the safety and longevity of individual organisms and collective species. Inappropriate expression of fear as well as prolonged exposure to stress, on the other hand, is maladaptive, leading to the development of serious psychological (e.g. depression and memory impairment) and physical (e.g. obesity and heart disease) disorders (Hammen, 2005; Tamashiro et al., 2011). It has long been recognized that OT plays an important role in learning and memory processes related to the fear response. For example, Bohus et al. (1978) provided the first evidence in this field showing that peripheral OT treatment facilitated extinction of learned avoidance behavior. Early research by Kovacs et al. (1978) also showed that intracerebroventricular (i.c.v.) administration of OT-antiserum increased the retention of passive avoidance behavior. More recent research suggests that OT modulates the stress response via an action on the hypothalamic–pituitary–adrenal (HPA) axis (Lukas and Neumann, in press; Parker et al., 2005). It is now also understood that distinct neuronal populations expressing γ-aminobutyric acid (GABA) in the CeA contribute substantially to OT’s effect on fear learning and its inhibitory action on stress (Huber et al., 2005; Viviani and Stoop, 2008). Knobloch et al. (2012), using in vitro optogenetics techniques, provided evidence that exposure to blue light of channelrhodopsin-2-expressing OT axonal projections from the PVN inhibited neurons in the output region of the CeA by activating a local GABAergic circuit. They further showed, using the same optogenetic technique in vivo, that stimulating endogenous OT release from PVN axonal projections in the CeA resulted in a robust decrease in freezing responses in
fear-conditioned rats (Knobloch et al., 2012). Interestingly, Ayers et al. (2011) recently provided evidence that peripheral but not central OT administration in rats was capable of reducing general states of anxiety associated with experimental procedures, but not conditioned fear. This evidence raises intriguing questions as to the specific mechanism of peripherally administered OT on fear and anxiety that should be explored further.

In humans, OT modulates a number of peripheral and neuronal processes related to threat. For example, Labuschagne et al. (2010) showed that an acute intranasal dose of OT (24 IU) attenuated amygdala hyperactivity resulting from the presentation of threatening stimuli (fearful faces) in patients with generalized social anxiety disorder. These investigators further showed that OT reduced medial frontal hyperactivity to negative stimuli (sad faces) in the same patient group (Labuschagne et al., 2011). Recent research shows that in human participants with impaired emotion regulation abilities, an intranasal dose (24 IU) of OT reduces social stress (public speaking)-induced increases in cortisol (Quirin et al., 2011). These findings support, and provide a neurocognitive basis for, preliminary research that outlined the potential of intranasal OT to reduce threat perception in socially anxious patients (Guastella et al., 2009). Taken together, the findings outlined here highlight the importance of OT in moderating fear and avoidance behaviors and point towards the need for further investigation into the use of OT as a treatment for patients with a variety of different anxiety disorders.

The role of OT in reward and approach behaviors

In contrast to fear and stress processes, the appropriate expression of approach behaviors such as mating, social bonding, and feeding is also important for ensuring the successful propagation of a species. It is for this reason that these behaviors are considered to be exceptionally rewarding and are learned with great efficiency. Emerging evidence implicates the OTergic system, in conjunction with dopamine (DA), for promoting behaviors such as pair bonding, and sexual arousal and appetite, and highlights a potential therapeutic benefit of OT in a number of DA-related disorders such as sexual dysfunction, autism, schizophrenia, and addiction (see Baskerville and Douglas, 2010 for review). Common OT and DA related brain regions involved in socio-sexual behaviors include the SON, PVN, MPOA, amygdala, NAcc, and the VTA. These brain regions maintain extensive shared OT and DA pathways known to regulate a broad range of reward processes (Skuse and Gallagher, 2009).

Over the past three decades, there have been an enormous number of studies outlining the role of OT in pair bonding and sexual behavior (see Donaldson and Young, 2008 for review). This research emerged largely out of pioneering work by Cort Pedersen and colleagues, who were the first to show that central administration of OT resulted in the induction of maternal behavior in virgin rats (Pedersen and Prange, 1979; Pedersen et al., 1982). Further, Sue Carter and colleagues provided the first evidence that centrally administered OT could facilitate monogamous pair-bond formation in prairie voles and later that centrally administered OT could modulate social interaction, aggression, and sexual satiety in prairie voles (Carter et al., 1992; Williams et al., 1992; Witt et al., 1990, 1992). Early findings from Julian Davidson’s group also outlined the ability of sexual self-stimulation to increase plasma OT levels in both healthy male and female humans (Carmichael et al., 1987).

A large portion of the research conducted into OT’s role in social and sexual behavior utilizes the prairie vole (Microtus ochrogaster) as the model organism (McGraw and Young, 2010). Prairie voles are a largely monogamous species that frequently form lifelong bonds with a partner after mating. A number of studies show that infusion of OT antagonists into the NAcc and prelimbic cortex (OTR and DA receptor rich brain areas highly associated with reward) can block pair bonding in prairie voles, while infusions of OT into the cerebral ventricles facilitate bonding (Williams et al., 1994; Young et al., 2001). Further studies with voles showed that DA modulation is also capable of altering pair bonding. For example, injections of the DA D2 receptor antagonist eticlopride prevents female voles from forming a bond with their male mate, while the D2 agonist quipiprole causes female voles to perform a significant partner preference even in the absence of mating (Gingrich et al., 2000). In contrast, the indirect DA receptor agonist amphetamine (AMPH) blocks pair bonding in male voles following mating with a female partner by stimulating D1-like, but not D2, receptors in the NAcc (Liu et al., 2010). Antagonizing D1-like DA receptors in the NAcc effectively rescues mating-induced partner preferences in AMPH-treated animals. These intriguing effects of OT on social behavior and bonding have also been extended to human populations.

The seminal work of Kosfeld and colleagues (2005) showed that OT nasal administration increased trusting behavior in humans, an effect that has been replicated and extended a number of times (Baumgartner et al., 2008; Cardoso et al., 2012; Van Ijzendoorn and Bakermans-Kranenburg, 2012). A range of studies using single doses of OT have also supported the conclusion that this neuropeptide enhances cognitive mechanisms (see Guastella and MacLeod, 2012 for review) involved in bonding and affiliation, including social communication (Ditzen et al., in press; Guastella et al., 2008a), the recognition of social cues (Lischke et al., 2012; Marsh et al., 2010), and the encoding of social memories (Guastella et al., 2008b; Rimmele et al., 2009). Several independent groups have also demonstrated that single doses of OT to teenagers and adult males with autism improve the processing and retention of social information (Hollander et al., 2007), improve emotion recognition when viewing the eye region of faces (Guastella et al., 2010), and increase trust and preference for social partners in a computer simulated ball game (Andari et al., 2010). Moreover, positive effects of a course of OT over several weeks also appear to improve social cognition in clinical disorders associated with social deficits (Feifel et al., 2012; Pedersen et al., 2011). Research evaluating the impact of intranasal OT administration on social cognition and behavior in drug-addicted humans, however, is currently lacking and represents an area of future research (see Pedersen et al., in press for very preliminary evidence).

The modulatory role of OT on psychostimulant effects

A large number of preclinical animal studies have outlined the effects of OT on the behavioral and neuronal activity induced by various drugs of abuse. Briefly, systemically administered OT dose-dependently attenuates tolerance to morphine and blocks naloxone-induced morphine withdrawal, inhibits tolerance to endogenous opioids (i.e. β-endorphin and Met-enkephalin) and cross-tolerance between two different opiates acting on the same µ-opioid receptors, and attenuates the maintenance (but not...
acquisition) of i.v. heroin self-administration (see Kovacs et al., 1998 for a thorough review). Studies using both central and peripheral routes of administration show that OT blocks tolerance to alcohol-induced hypothermic, myorelaxant, and akinesic effects (Jodogne et al., 1991; Szabo et al., 1989), decreases the severity of alcohol withdrawal symptoms (Szabo et al., 1987), and attenuates alcohol self-administration (Bowen et al., 2011). A clinical trial of intranasal OT treatment in alcohol dependent patients provided preliminary evidence for OT blocking withdrawal symptoms in this group (Pedersen et al., in press). Both central and peripheral OT administration has been shown, in a dose-dependent manner, to attenuate cocaine-induced locomotor hyperactivity (Kovacs et al., 1990), exploratory hyperactivity (Sarnyai et al., 1990), stereotyped behavior (Sarnyai et al., 1991), tolerance (Sarnyai et al., 1992), and i.v. self-administration (Sarnyai and Kovacs, 1994). This extensive body of research has provided convincing evidence for OT acting on OTRs in a number of brain regions including the NAcc, amygdala, hippocampus, and the olfactory bulbs to alter drug-induced DA activity. The central role of OT in altering drug-induced behaviors has been confirmed by numerous studies that have injected microgram doses of OT into the brain to influence behavior, and others in blocking the inhibitory behavioral effects of peripherally administered OT with centrally applied OTR antagonists (Kovacs et al., 1998; Sarnyai, 1998; Sarnyai and Kovacs, 1994; Sarnyai et al., 1991). Given that other reviews have thoroughly outlined research on the modulatory role of OT on psychostimulant effects with a specific focus on cocaine, we will only briefly discuss this research in order to set the stage for a more thorough review of the interaction between OT and amphetamine-type stimulants.

OT and cocaine: Preclinical and preliminary clinical research

Cocaine is a widely used drug of abuse with characteristic CNS psychostimulant effects. It exerts its action primarily via catecholamines (DA and noradrenaline (NA)) and to a lesser extent serotonin (5-HT) to enhance activity of neurons in the brain’s reward circuitry (Uhl et al., 2002). Cocaine is considered to act primarily by binding to DA transporters (DATs) to inhibit the action of the reuptake pump, resulting in increased levels of DA in the synaptic cleft (Zahniser and Sorkin, 2009). The effects of OT on cocaine-induced behavior and associated neuronal activity have been studied extensively in rodent models. For example, Kovacs et al. (1990) showed that systemic injections of OT (1.0 and 5.0 µg/animal, subcutaneous, s.c.) 15 min prior to cocaine (30 mg/kg, s.c.) injections prevented the utilization of dopamine in the NAcc, but not nucleus caudatus, and decreased locomotor hyperactivity in mice. Sarnyai (1993) further showed that OT administered systemically (0.5 and 5.0 µg/animal, s.c.) and centrally (10 and 50 ng/animal, i.c.v.) 60 min prior to cocaine (15 mg/kg, s.c.) attenuated stereotyped sniffing behavior in rats. Interestingly, the systemic doses of OT (5.0 µg/animal, s.c.) that are capable of inhibiting cocaine-induced stereotyped sniffing behavior have no effect on cocaine-induced grooming behavior. Sarnyai (1998) maintains that the diverging effects of OT on sniffing and grooming behavior can be explained, in part, by these two behaviors being mediated by distinct DAergic brain regions (i.e. the mesolimbic and nigrostriatal systems, respectively). In order to determine the distinct brain regions responsible for OT’s effect on blocking cocaine-induced sniffing, Sarnyai (1993) injected OT (100 pg/animal) directly into mesolimbic and nigrostriatal brain regions 60 min prior to cocaine (15 mg/kg, s.c.) treatment. He showed that OT injected directly into the NAcc and tuberculum olfactorium, but not the nucleus olfactorius, CeA, or nucleus caudatus, inhibited cocaine-induced sniffing. In a thorough and informative review of OT and drug addiction, Kovacs and colleagues (1998) suggest that the ability of OT to block cocaine-induced behavioral effects likely results from the inhibitory action of OT on DA utilization and release, and on postsynaptic DA receptors across a network of limbic and basal forebrain structures. Since these important discoveries, a large body of evidence has also outlined the effects of cocaine on endogenous OT activity and highlighted the impact of these changes on important behavioral processes.

Josephine John’s group showed that chronic gestational and post-gestational cocaine treatment in rat dams results in disruptions in the onset of maternal behavior (e.g. pup retrieval and grooming), increases aggression directed toward an intruder, decreases OT levels in the MPOA, VTA, and hippocampus, and decreases OTR binding density in the VMH and BNST (Jarrett et al., 2006; Johns et al., 1997a,1997b). The detrimental effects of gestational cocaine treatment also appear to be long lasting, with young adult female offspring of cocaine-treated dams exhibiting higher levels of aggression associated with lower levels of OT in the amygdala (McMurray et al., 2008). It is highly likely that these generational effects can be attributed to both gestational cocaine exposure in utero and maladaptive rearing conditions. These preclinical findings have also been extended to humans. Light et al. (2004) provided evidence that mothers who used cocaine during pregnancy showed lower plasma OT levels, greater hostility and depressed mood, and less social support and adaptive coping strategies for stressful life events compared to cocaine-naïve mothers. Interestingly, cocaine exposed mothers also maintained higher ambulatory blood pressure and urinary norepinephrine levels, while urinary cortisol and epinephrine levels were blunted, suggesting impairments in the HPA axis stress system. Despite an immense amount of evidence outlining the relationship between OT and cocaine, subsequent research has only recently begun to provide insights into the interaction between OT and other psychostimulants.

OT and meth/amphetamine: Preclinical and preliminary clinical research

The amphetamines METH and AMPH are highly potent and commonly abused psychostimulants that share almost identical chemical structures. Despite their widespread use and serious detrimental effects on both physical and mental health, there are no effective pharmacological or psychological treatments currently available (Kaye et al., 2008; Lee and Rawson, 2008; Rose and Grant, 2008). Similar to cocaine, amphetamines primarily exert their action on DA, NA, and to a lesser extent 5-HT (Sulzer et al., 2005). Early research into the role of the adrenergic system in regulating neurohypophysial hormones showed that administration of a moderate dose (5 mg/kg, intraperitoneal (i.p.)) of AMPH to rats significantly decreased hypothalamic and neurohypophysial OT content (Guzek et al., 1978). Given that this study did not specifically assess the effects of AMPH on the adrenergic system, it is...
highly likely that other neurotransmitters such as DA played a significant role. Interestingly, in the late 1970s, it was shown that central administration of OT (50 and 100 µg/animal, i.c.v.) in rats with ipsilateral 6-hydroxy DA lesions in the SN caused ipsilateral rotational behavior towards the lesioned side. Systemic injections of AMPH also caused this behavior, and the researchers postulated that OT caused presynaptic activation of the nigrostriatal DAergic terminals to influence motility (Schulz et al., 1979).

To investigate the effects of OT on the behavioral actions of AMPH in mice, Kovacs et al. (1985) used graded doses (0.5, 5.0, and 50 µg, s.c.) of OT administered systemically 60 min prior to an injection of AMPH (1 mg/kg, s.c.) and measured locomotor activity. In contrast to the effects of similar doses of OT on cocaine-induced behavior outlined above, none of the doses of OT had an effect on AMPH-induced locomotor hyperactivity. Using the same doses, administration route, and time-course of OT and AMPH as in the previously described study, Sarnyai (1993) assessed whether OT inhibited AMPH-induced stereotyped sniffing behavior in rats. This study also failed to show an effect of OT.

Differences in the pharmacological action of amphetamines and cocaine might help to explain the discrepancies between OT’s effect on these drugs. Cocaine is a relatively short half-life drug that acts quite selectively to increase synaptic DA levels by inhibiting the action of DAT. In addition to blocking the reuptake of DA by inhibiting the action of DAT, amphetamines actually reverse the DAT pump to substantially increase DA release from presynaptic terminals. Further still, amphetamines inhibit the metabolism of DA by blocking the action of monoamine oxidase. As a result, amphetamines maintain relatively long half-lives of around 12 hours, depending on dose (see Cruickshank and Dyer, 2009 for review). Given the prolonged action of amphetamines, it is likely that higher doses of OT and a more proximal time-course of administration might be required before an effect can be observed.

The extended action of amphetamines on neuronal DA activity has also been linked to a wide range of stereotyped and psychotic symptoms in both animal models and humans (Hermens et al., 2009). Interestingly, accumulating evidence suggests that dysregulation of the OTerGic system may also be associated with the development of symptoms of schizophrenia (Goldman, 2009). In order to investigate a possible role for OT as an antipsychotic agent, Feifel and Reza (1999) administered graded doses (0, 0.04, 0.2, 1 mg/kg, s.c.) of OT, immediately prior to AMPH (2 mg/kg, s.c.) in rats and then tested them on the prepulse inhibition (PPI) task. PPI is a well-validated test of sensorimotor gating in which animals are presented with an intense startling stimulus ("pulse") that is immediately preceded by a weaker stimulus ("prepulse"). Depending on prepulse intensity and inter-pulse intervals animals typically reduce their startle response to the test pulse following presentation of the prepulse. However, patients with schizophrenia often show deficits in PPI and this can be modeled by administration of psychostimulants such as AMPH to laboratory animals. Accordingly, in Feifel and Reza’s study, AMPH significantly impaired PPI, with the highest dose of OT (1 mg/kg) successfully reducing this effect. These results suggest that OT is capable of reversing some of the psychotic symptoms associated with this disorder (Feifel et al., 2010, 2012; Pedersen et al., 2011). Further investigation might determine how OT achieves this effect as PPI is considered to rely on a number of neuronal processes including DA and glutamate (GLU) neurotransmission (Braff, 2010). Feifel and Reza’s (1999) study also indicates that relatively high systemic doses of OT and/or a more proximal time-course of administration are required to effectively compete with AMPH’s action on brain and behavior. However, large doses of OT (e.g. 1 mg/kg) delivered systemically have been shown to cause sedation and thus caution should be taken in the interpretation of findings such as these (Uvnás-Moberg et al., 1994). That is, it is possible that systemically administered OT may result in non-specific sedative effects such as opposed to specifically blocking stimulant-induced behaviors. As outlined above, OT causes a massive release of the inhibitory neurotransmitter GABA from neurons in the CeA and has also been found to facilitate the effects of sedating anxiolytics such as diazepam (Viviani et al., 2010). Interestingly, central administration of a novel non-peptide OT agonist WAY-267464, produced by Wyeth (now part of Pfizer), has recently been shown to have a similar anxiolytic profile to OT on a number of behavioral (i.e. four-plate test, elevated zero maze) and autonomic (i.e. stress-induced hyperthermia) measures and also significantly reverses disruption in PPI of the acoustic startle reflex produced by AMPH (Ring et al., 2010). However, the extent to which this drug’s selectivity to OT receptors has recently been contested (Hicks et al., 2012).

Recent research has examined the effects of OT in specific brain regions and investigated how this impacts on neurotransmitter systems involved in the formation of METH-induced locomotor hyperactivity in mice. Qi et al. (2008) used microdialysis linked with high performance liquid chromatography (HPLC) to detect changes in monoamine activity in the striatum, NAcc, and prefrontal cortex (PFC) following METH and/or OT administration. Central OT (0.1, 0.5, and 2.5 µg/mouse, i.c.v.) had no effect on locomotor activity in drug naïve animals, but when administered 30 min prior to METH (2 mg/kg, i.p.), it significantly reduced locomotor hyperactivity in a dose-dependent manner. Compared with METH administration alone, co-administration of OT (2.5 µg/mouse) and METH produced markedly reduced ratios of the DA metabolites 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA) to DA in the NAcc and striatum, indicating decreased DA metabolism. Central administration of the OTR antagonist atosiban (2 µg/mouse, i.c.v.) attenuated these effects, suggesting that OT exerted its inhibitory effects on METH via OTRs.

Following on from this research, Qi et al. (2009) examined OT effects on METH-induced conditioned place preference (CPP). CPP is a well-validated test of drug reward in which animals are administered a substance in a specific environment (i.e. a place) and later show a preference for this place over one in which they receive only vehicle injections. In this experiment, centrally administered OT (2.5 µg/mouse, i.c.v.) 30 min prior to METH (2 mg/kg, i.p.) significantly inhibited the acquisition of a place preference for METH, but had no effect on the expression of an already acquired CPP for METH. A variety of doses of OT (0.1, 0.5, and 2.5 µg/mouse, i.c.v.) also facilitated the extinction of METH-induced CPP. These doses of OT also abolished the reinstatement of CPP induced by restraint-stress, but not METH (1 mg/kg, i.p.) challenge. The content of medial PFC (mPFC) GLU was determined by microdialysis coupled to HPLC with results...
showing that OT inhibited GLU activity in this brain region following restraint stress-, but not METH (1 mg/kg, i.p.) challenge-, induced reinstatement of CPP. Again, these inhibitory effects of OT could be prevented by central administration of atosiban (2 µg/mouse, i.c.v.). This work outlines the action of OT on METH-related behaviors and associated neuronal activity and provides insights into the role of OT on modulating METH-induced neuronal activity via neurotransmitter systems other than DA. A large body of evidence now suggests that GLU activity is associated with learning, memory, stress, and reward process, which are known to impact on the formation of substance abuse disorders (Cleva et al., 2010).

Although CPP is considered to be a robust model of drug reward-related behavior, it is widely accepted that drug self-administration is a more ecologically valid model of addiction (Ahmed, 2012). A recent study examined the effects of peripherally administered OT on METH self-administration in rats (Carson et al., 2010a). Animals were trained for 11 days to press a lever for METH (i.v. jugular vein cannulation) on a progressive ratio, and were then given escalating systemic doses (0.001, 0.01, 0.1, 0.3 and 1 mg/kg, i.p.) of OT or saline (SAL) 30 min prior to daily self-administration sessions. The initial lower doses of OT were chosen as these matched the doses shown in earlier research to successfully modify cocaine-induced behaviors, including cocaine self-administration, via a similar peripheral administration route (s.c.) (Sarnyai and Kovacs, 1994). Not surprisingly, and in parallel to earlier similar studies using AMPH, these lower doses did not impact on METH self-administration. Strikingly, the higher doses (0.3 and 1 mg/kg) of OT significantly reduced lever pressing for METH self-administration with an almost complete absence of responding at the highest dose (Figure 2(a) and (b)). These doses of OT also reduced reinstatement of extinguished METH-seeking behavior caused by METH (1 mg/kg, i.p.) challenge (Figure 2(c)). Following a 10-day washout period, blood samples taken from these animals provided evidence that systemic OT treatment significantly increased plasma OT concentration compared with animals treated with METH or SAL alone (Figure 2(d)). This latter finding provides further support for the self-stimulating

Figure 2. Systemic (intraperitoneal) injections of oxytocin (OT) inhibit lever-press (a) responding for intravenous infusions (b) of methamphetamine (METH) and block METH-induced reinstatement (c) of lever-press responding in rats. Plasma oxytocin levels following a 10-day washout period from rats either treated with daily injections of saline (SAL) or that self-administered METH and were treated with either saline (SAL/METH) or increasing daily doses of oxytocin (OT/METH) (d).

*Strong trend.
+<0.05.
**<0.01.
***<0.001.

Figure 3. The distribution of Fos immunoreactive cells (black dots) and oxytocin expressing neurons (amber immunoprecipitate) in the supraoptic nucleus (SON; (a), (c), (e), (g)) and the paraventricular nucleus of the hypothalamus (PVN; (b), (d), (f), (h)) from representative rats treated with saline/saline (SAL/SAL; (a), (b)), saline/oxytocin (SAL/OXY; (c), (d)), saline/methamphetamine (SAL/SAL; (e), (f)), and oxytocin/methamphetamine (OXY/METH; (g), (h)). Pre-treatment with oxytocin increased Fos immunoreactivity in oxytocin positive cells in the SON and PVN. The black arrow depicts Fos only labeling and the white two-headed arrow depicts Fos and oxytocin double-labeling. Scale bar: 100 µm ((a), (c), (e), (g)) and 200 µm ((b), (d), (f), (h)).

opt: optic tract; 3V: third ventricle.

Figure adapted from Carson DS, Hunt GE, Guastella AJ, et al. (2010b) Systemically administered oxytocin decreases methamphetamine activation of the subthalamic nucleus and accumbens core and stimulates oxytocinergic neurons in the hypothalamus. Addict Biol 15: 448–463 with permission from John Wiley & Sons, Inc.
action of OT and suggests that systemic administration of OT is capable of upregulating the endogenous OT system. Notably, METH administered alone had no effect on plasma OT levels.

In separate experiments, OT (0.3 and 1 mg/kg, i.p.) successfully inhibited METH-induced (1 mg/kg, i.p.) locomotor hyperactivity (Carson et al., 2010a). Taken together, these findings provide the first evidence that systemically applied OT could significantly inhibit METH-induced behaviors. The use of a peripheral route of OT administration is an important aspect of this research as it is much more clinically relevant than central administration, a delivery modality that is highly unlikely to find a place in clinical practice. As mentioned previously, systemic injections of OT may be capable of crossing the BBB in small to moderate quantities (Ermisch et al., 1985; Landgraf et al., 1979). Once in the brain, even small quantities of OT may bind to OTRs on OT containing neurons in the PVN and SON thus stimulating release of significant quantities of endogenous OT to trigger a feed-forward response (Moos et al., 1984; Rossoni et al., 2008).

To further examine the inhibitory effects of OT on METH-related behaviors, c-Fos immunohistochemistry was used to determine the neuronal activation accompanying the co-administration or individual administration of OT and METH (Carson et al., 2010b). In this study, four groups (SAL/SAL; METH/SAL; SAL/OT; METH/OT) of rats were utilized in order to highlight the effects of OT on METH-induced behavioral and neuronal activity, as well as to determine the effects of systemically administered OT alone on behavior and brain activity. The most prominent finding in this study was that OT (2 mg/kg, i.p.) significantly reduced METH-induced (2 mg/kg, i.p.) c-Fos expression in the subthalamic nucleus (STh) and the NAcc core, two regions of the basal ganglia that are highly implicated in impulse control and drug addiction (Eagle and Baunez, 2010).

Another important result was that OT (2 mg/kg), when peripherally administered alone, increased c-Fos expression in a number of brain regions including the SON, PVN, CeA, lateral parabrachial nucleus, and the locus coeruleus. These are all OTR dense brain regions implicated in a number of physiological processes including reproduction, anxiety, water balance, blood osmolality, and sleep. A double-labeling approach showed that peripherally administered OT increased c-Fos activation within OT containing neurons of the SON and PVN, further supporting previous observations that OT is capable of stimulating its own release from central sites (Moos et al., 1984) (Figure 3). Interestingly, unlike previous findings that showed MDMA could stimulate central and peripheral OT release in rats (Thompson et al., 2007), this study showed no effect of METH on stimulating hypothalamic OT neurons (Carson et al., 2010b). These findings are also in further support of the study outlined above that showed no effect of METH treatment on plasma OT levels (Carson et al., 2010a).

The study by Carson et al. (2010b) further showed that co-administration of OT and METH increased c-Fos activity within a number of sites including the NAcc shell, median preoptic nucleus, MPOA, paraventricular anterior thalamic nucleus, and the medial amygdala (MeA) relative to either drug alone. The NAcc shell, MPOA, and MeA are brain regions highly implicated in reward and sexual behavior, suggesting that OT may be capable of shifting motivation and behavior from addiction to social/sexual behavior (Hull and Dominguez, 2007; McGregor et al., 2008). There were, however, no differences in c-Fos activity in SON or PVN OT containing neurons in rats co-administered METH and OT compared with OT alone. This study also provided impressive evidence for a time-dependent effect of OT on inhibiting METH-induced locomotor hyperactivity with OT exerting its effects for over 60 minutes (Figure 4).

Following directly on from this study, the effects of systemic OT administration or intracranial (i.c.) microinjections of OT in the STh and NAcc core on preventing METH-induced CPP were investigated (Baracz et al., 2011). A pretreatment of systemic OT (0.6 mg, i.p.) or OT (0.6 ng, i.c.) microinjected into the STh or the NAcc core 10 min prior to METH (1 mg/kg, i.p.) administration attenuated the formation of a CPP for METH. This provides further support for the evidence that both the STh and NAcc core are critically involved in the inhibitory effect of OT on the rewarding
properties of METH. A very recent study conducted by Baracz and Cornish (in press) provided important insights into the key neurotransmitter systems responsible for reward learning in the STh. They showed that a single-dose of DA (100 nmol/side) injected directly in to the STh resulted in a significant CPP and that the mixed DA receptor antagonist fluphenazine (10 nmol/side) or OT (0.6 nmol/side) administered in to the STh blocked this effect. The selective OT antagonist desGly-NH2.d(CH2)5[D-Tyr2,Thr4]JOTV reversing the inhibitory action of OT on DA reward learning in the STh providing strong support for local OTRs in the STh having an inhibitory action on DAergic reward processes associated with psychostimulant drug effects. The researchers point out that although evidence exists for OT mRNA in the STh it is currently unclear whether these receptors are located pre- or post-synaptically making it difficult to determine the specific action of OT on DA activity in this brain region.

To further elucidate the effects of OT on METH-induced neuronal activity at the neurotransmitter and receptor level, Qi et al. (2012) measured mPFC and dorsal hippocampus (DHC) GLU and GABA activity using in vivo microdialysis coupled with HPLC and fluorescence detection in freely moving mice. They showed that OT (2.5 µg/µL per mouse, i.c.v.) administered alone had no effect on basal GLU levels, but attenuated GLU increases in the mPFC and decreases in the DHC when administered 10 min prior to METH (2 mg/kg, i.p.). OT was also capable of increasing basal GABA levels in the mPFC and DHC, and inhibited METH-induced decreases in DHC GABA activity. Further still, this study provided evidence that OT significantly attenuated METH-induced GLUergic receptor (NR1 subunit) expression in the PFC whilst increasing METH-induced GLUergic transporter (GLT1) activity in the hippocampus. Qi et al. additionally replicated their previous findings that OT potently suppressed METH-induced hyperlocomotion. The authors also provided impressive evidence that OT exerted its effects on both the brain and behavior induced by METH over a period of several hours. As with previous studies from this group, central administration of atosiban (10 µg/µL per mouse, i.c.v.) blocked the inhibitory effects of OT on both METH-induced neuronal activity and hyperlocomotion, suggesting again that OT likely exerted its effects on OTRs. Table 1 outlines the effects of oxytocin administration on meth/amphetamine related behavior and brain activity.

It is clear from the extensive research outlined above that OT has a powerful effect on blocking many behavioral and neuronal processes related to METH intoxication. There is now an urgent need to outline the role of OT in human METH intoxication and to begin to investigate its efficacy as a treatment for METH dependence. One recent preliminary study aimed to determine the effects of chronic METH use on the OThergic system in human METH addicts. In this study, blood samples were collected from a naturalistic sample of METH poly-drug users that met DSM-IV criteria for METH dependence/abuse (Carson et al., 2012a). The blood samples were examined for levels of a variety of different drugs of abuse and plasma OT, AVP, and cortisol were assessed relative to healthy non-METH using controls that were matched on a range of demographic variables. A number of psychiatric (positive, negative, depressive, manic, and disorientation symptoms) and personality (anti-social personality disorder and impulsivity) variables were also examined. Analysis of endogenous levels of OT in this patient group is important when considering both the relationship between OT and METH related behaviors, and also deficits in peripheral OT levels amongst other patient groups. For example, patients diagnosed with depression were shown to have lower plasma OT levels compared with controls and that this was associated with both severity of depression and anxiety symptoms (Scantamburlo et al., 2007). Further, patients with autism showed lower plasma OT than matched controls and had lower levels of OT precursor peptides, indicating an excess of the immature form of OT (Al-Ayadhi, 2005; Green et al., 2001; Modahl et al., 1998). Interestingly, OT administered to patients with autism reduced associated symptoms such as repetitive and stereotyped behaviors and improved patients’ social communication (Andari et al., 2010; Guastella et al., 2010; Hollander et al., 2003, 2007). The effect of OT on repetitive behaviors in autism is interesting when considering that psychostimulants dramatically increase stereotyped behaviors such as head weaving, sniffing, and hyperlocomotion in rodents and OT significantly reduces these effects (Carson et al., 2010a, 2010b; Sarnyai, 1998). Carson et al. (2012a) showed in their study that plasma OT and AVP levels were similar in both METH users and controls. However, there were significantly lower cortisol levels in the METH using group. These latter findings echo those observed in chronic cocaine use and suggest a dysregulation in the HPA axis (Light et al., 2004). There were no correlations between psychiatric symptomatology or toxicology data and neuroendocrine levels. The lack of change in OT plasma levels in this group is in line with the previously discussed preclinical research that showed METH had no effect on altering either plasma or hypothalamic OT levels (Carson et al., 2010a, 2010b).

**Oxytocin and MDMA: Preclinical and clinical research**

The amphetamine-type stimulant MDMA is a widely used psychostimulant drug with some psychedelic properties. In contrast to cocaine and typical amphetamines, MDMA acts primarily on neuronal 5-HT with some catecholamine activity (Cole and Sumnall, 2003; Green et al., 2003; Kalant, 2001; Sulzer et al., 2005). During the 1970–1980s, MDMA was informally trialed in California’s Bay Area as an adjunct to psychotherapy before being banned by most governments globally due to concerns relating to 5-HTergic neurotoxicity and widespread use amongst young people in the rave/dance music scene (Carson et al., 2012b). Although many advocates for the decriminalization of MDMA maintain that it is safe and well tolerated, there is some evidence that its misuse, under certain conditions, can result in potentially fatal hyponatraemia and that this may be related to the antidiuretic action of OT and AVP (Campbell and Rosner, 2008; Sessa, 2007). Initial in vitro work by Forsling et al. (2002) showed that MDMA, when applied to isolated rat hypothalamus, resulted in substantial increases in OT and AVP release. These findings have been replicated in humans whereby MDMA positive dance party-goers showed increased plasma AVP and OT levels (Wolff et al., 2006). Wolff et al. also linked these increases in neurohypophysial hormones to changes in plasma osmolality and plasma sodium levels and suggested that MDMA use could be dangerous if hypotonic (e.g. water) and not isotonic fluid (e.g. sports drinks) was excessively consumed while intoxicated and dancing in hot sweaty conditions (see also (Hargreaves et al., 2007)). Importantly, however, there is actually minimal evidence that MDMA maintains a high abuse potential or that its use is dangerous if simple precautions are adhered to (Degenhardt et al., 2010; Morgan et al., 2010; Nutt, 2009). In fact there is now a growing body of research that
increased OTR levels. It is possible that the changes in OT resulted in increased hypothalamic OT levels and GHB resulted in detected eight weeks post drug treatment. Interestingly, MDMA object recognition but no changes in monoamine levels were testing, all of the animals showed reduced social interaction and hypothalamic OT and OTR levels were also assessed. During week period. Monoamine levels in the cortex and striatum and were assessed on a variety of measures including the emergence consecutive days. After a four-week washout period, animals have also been confirmed by a recent study that outlined the ability of MDMA to rats, there was a substantial increase of activity in thalamus, or CeA, suggesting that MDMA's action on OT release is mediated specifically by 5-HT receptors. These findings strongly suggest that MDMA's prosocial effects and action on OT are mediated by 5-HT receptors. These results strongly suggest that MDMA's prosocial effects and action on OT are mediated by 5-HT receptors. These findings have also been confirmed by a recent study that outlined the ability of WAY 100,635 to inhibit MDMA stimulated c-Fos activity in the SON and PVN but did not alter c-Fos activity in the striatum, thalamus, or CeA, suggesting that MDMA's action on OT release is mediated specifically by 5-HT receptors (Hunt et al., 2011). Further research is needed to determine the specific relationship between OT and 5-HT systems in the brain and how this relates to social behavior (Hammock et al., 2012).

In an attempt to uncover the action of MDMA on brain and behavior at the neuropeptide level, Thompson et al. (2007) outlined the role of OT in the expression of social behavior and neuronal activity following MDMA administration in rodents. Following administration of a moderate dose (5 mg/kg, i.p.) of MDMA to rats, there was a substantial increase of activity in hypothalamic OT containing neurons as measured by c-Fos immunohistochemistry as well as an increase in plasma OT levels that were associated with increased social interaction. These effects were inhibited by administration of both the 5-HT₁₅ receptor agonist WAY 100,635 and the OTR antagonist tocinoic acid. These results strongly suggest that MDMA's prosocial effects and action on OT are mediated by 5-HT receptors. These findings have also been confirmed by a recent study that outlined the ability of WAY 100,635 to inhibit MDMA stimulated c-Fos activity in the SON and PVN but did not alter c-Fos activity in the striatum, thalamus, or CeA, suggesting that MDMA’s action on OT release is mediated specifically by 5-HT receptors (Hunt et al., 2011). Further research is needed to determine the specific relationship between OT and 5-HT systems in the brain and how this relates to social behavior (Hammock et al., 2012).

<table>
<thead>
<tr>
<th>Drug</th>
<th>Behavioral assay</th>
<th>Effect of OT</th>
<th>Route of OT administration</th>
<th>Sites of action</th>
<th>Neurotransmitter system</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphetamine</td>
<td>Locomotor hyperactivity</td>
<td>None</td>
<td>s.c.</td>
<td>Not assessed</td>
<td>Not assessed</td>
<td>Kovacs et al. (1985)</td>
</tr>
<tr>
<td>Amphetamine</td>
<td>Stereotyped sniffing</td>
<td>None</td>
<td>s.c.</td>
<td>Not assessed</td>
<td>Not assessed</td>
<td>Sarnyai (1993)</td>
</tr>
<tr>
<td>Amphetamine</td>
<td>Prepulse inhibition</td>
<td>Increased</td>
<td>s.c.</td>
<td>Not assessed</td>
<td>Not assessed</td>
<td>Feifel and Reza (1999)</td>
</tr>
<tr>
<td>Methamphetamine</td>
<td>Conditioned place preference</td>
<td>Decreased; blocked stress-induced reinstatement</td>
<td>i.c.v.</td>
<td>NAcc; striatum</td>
<td>Dopamine</td>
<td>Qi et al. (2008)</td>
</tr>
<tr>
<td>Methamphetamine</td>
<td>Locomotor hyperactivity</td>
<td>Decreased</td>
<td>i.c.v.</td>
<td>mPFC</td>
<td>Glutamate</td>
<td>Qi et al. (2009)</td>
</tr>
<tr>
<td>Methamphetamine</td>
<td>Self-administration</td>
<td>Decreased; blocked methamphetamine-primed reinstatement</td>
<td>i.p.</td>
<td>Not assessed</td>
<td>Not assessed</td>
<td>Carson et al. (2010a)</td>
</tr>
<tr>
<td>Methamphetamine</td>
<td>Conditioned place preference</td>
<td>Decreased</td>
<td>i.p.</td>
<td>STH; NAcc Core</td>
<td>Not assessed</td>
<td>Carson et al. (2010b)</td>
</tr>
<tr>
<td>Methamphetamine</td>
<td>Locomotor hyperactivity</td>
<td>Decreased</td>
<td>i.c.</td>
<td>STH; NAcc Core</td>
<td>Not assessed</td>
<td>Barac et al. (2011)</td>
</tr>
</tbody>
</table>

OT: oxytocin; s.c.: subcutaneous; i.c.v.: intracerebroventricular; i.p.: intraperitoneal; i.c.: intracranial; NAcc: nucleus accumbens; mPFC: medial prefrontal cortex; STH: subthalamic nucleus; DHC: dorsal hippocampus; GABA: γ-aminobutyric acid

suggests MDMA has enormous potential as an adjunct to psychotherapy in treatment resistant psychiatric disorders, including addiction (Jerome et al., in press; Mittoener et al., 2013; Oehen et al., 2013).

In an attempt to uncover the action of MDMA on brain and behavior at the neuropeptide level, Thompson et al. (2007) outlined the role of OT in the expression of social behavior and neuronal activity following MDMA administration in rodents. Following administration of a moderate dose (5 mg/kg, i.p.) of MDMA to rats, there was a substantial increase of activity in hypothalamic OT containing neurons as measured by c-Fos immunohistochemistry as well as an increase in plasma OT levels that were associated with increased social interaction. These effects were inhibited by administration of both the 5-HT₁₅ receptor agonist WAY 100,635 and the OTR antagonist tocinoic acid. These results strongly suggest that MDMA’s action on OT are mediated by 5-HT receptors. These findings have also been confirmed by a recent study that outlined the ability of WAY 100,635 to inhibit MDMA stimulated c-Fos activity in the SON and PVN but did not alter c-Fos activity in the striatum, thalamus, or CeA, suggesting that MDMA’s action on OT release is mediated specifically by 5-HT receptors (Hunt et al., 2011). Further research is needed to determine the specific relationship between OT and 5-HT systems in the brain and how this relates to social behavior (Hammock et al., 2012).

In order to assess the potential lasting effects of MDMA on brain and behavior at the neuropeptide level, Thompson et al. (2007) outlined the role of OT in the expression of social behavior and neuronal activity following MDMA administration in rodents. Following administration of a moderate dose (5 mg/kg, i.p.) of MDMA to rats, there was a substantial increase of activity in hypothalamic OT containing neurons as measured by c-Fos immunohistochemistry as well as an increase in plasma OT levels that were associated with increased social interaction. These effects were inhibited by administration of both the 5-HT₁₅ receptor agonist WAY 100,635 and the OTR antagonist tocinoic acid. These results strongly suggest that MDMA’s action on OT are mediated by 5-HT receptors. These findings have also been confirmed by a recent study that outlined the ability of WAY 100,635 to inhibit MDMA stimulated c-Fos activity in the SON and PVN but did not alter c-Fos activity in the striatum, thalamus, or CeA, suggesting that MDMA’s action on OT release is mediated specifically by 5-HT receptors (Hunt et al., 2011). Further research is needed to determine the specific relationship between OT and 5-HT systems in the brain and how this relates to social behavior (Hammock et al., 2012).

In order to assess the potential lasting effects of MDMA and γ-hydroxybutyrate (GHB) alone and in combination, van Nieuwenhuijzen et al. (2010) administered MDMA (5 mg/kg, i.p.) and GHB (500 mg/kg, i.p.) or their combination to rats over 10 consecutive days. After a four-week washout period, animals were assessed on a variety of measures including the emergence test, social interaction, and object recognition tasks over a two-week period. Monoamine levels in the cortex and striatum and hypothalamic OT and OTR levels were also assessed. During testing, all of the animals showed reduced social interaction and object recognition but no changes in monoamine levels were detected eight weeks post drug treatment. Interestingly, MDMA resulted in increased hypothalamic OT levels and GHB resulted in increased OTR levels. It is possible that the changes in OT neurobiology may reflect a compensatory response from repeat dosing with MDMA and GHB which may act to moderate some of the detrimental effects of these drugs.

The preclinical evidence linking MDMA’s prosocial effects to OT has been translated to humans. A laboratory based human trial showed that single doses of MDMA increase plasma OT and that this is associated with increases in self-reported amicability (Dumont et al., 2009). In this study, 15 healthy participants were administered MDMA (100 mg) or placebo orally using a double-blind, randomized, placebo controlled, cross-over design. MDMA induced a significant increase in plasma OT and increased levels of reported prosocial feelings (amicability). Within subjects, the changes in prosocial feelings were robustly and positively correlated with variations in OT plasma levels.

A very recent study also outlined the effects of MDMA on complex emotion recognition using the Reading the Mind in the Eyes Task (Hysek et al., 2012). This study used 48 healthy volunteers (24 men and 24 women) in a double-blind, placebo controlled, within-subjects design. The findings of this study showed that orally administered MDMA (125 mg) was capable of enhancing accuracy of mental states decoding for positive stimuli (e.g. friendly) but impaired mental states decoding for negative stimuli (e.g. hostile). Interestingly, a study by Bedi et al. (2010) also showed that MDMA (1.5 mg/kg) robustly decreased accuracy of facial fear recognition. Further, Hysek et al. showed that MDMA significantly increased plasma OT and cortisol levels and subjective prosocial behavior. Together, the research outlined here has important implications for the use of MDMA as a therapeutic intervention for psychiatric disorders (e.g. autism, PTSD, social anxiety disorder, and addiction) and warrants further investigation.

**Conclusions**

OT is clearly an important neuropeptide which is involved in the control of a broad number of critical physiological and psychological processes. It is interesting to consider that OT may be capable of enhancing the focus on prosocial adaptive behaviors while at the same time reducing the abuse potential of addictive
drugs. Future research might now aim to determine the specific role of OT in social and cognitive deficits following chronic methamphetamine administration in both animal models and humans. Although much of the specific underlying neuronal and behavioral processes of OT on drug-related behavior are still to be uncovered, this research is now at a stage where clinical trials of intranasal OT are urgently needed. A critical step in OT’s progression as a therapeutic agent in psychiatry is the effective translation of preclinical animal models into well-controlled human clinical trials. Further, development of novel OT agonists that provide enhanced BBB permeability and selectivity to central OT receptors are an exceptionally important aspect of this research and should be watched closely for emerging developments. Additionally, it is interesting to consider the potential therapeutic role of MDMA in psychiatry and that its effects may be mediated by an OT/5-HT interaction. Future MDMA treatment trials in psychiatric populations, such as those being conducted by the Multidisciplinary Association for Psychedelic Studies, may benefit from analyzing changes in both OT and monoamines such as 5-HT and how this is linked to improvements in psychosocial functioning.

Funding

This research was supported by a National Health and Medical Research Council Biomedical Scholarship (633120) and an Australasian Research Council Professorial Fellowship (DP0988069).

Conflict of interest

The authors declare that there are no conflict of interest.

References


Sofroniew MV, Weindl A, Schrell U, et al. (1981) Immunohistochemistry of vasopressin, oxytocin and neurophysin in the hypothalamus and


