Review article

The neurocircuitry involved in oxytocin modulation of methamphetamine addiction

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A B S T R A C T
The role of oxytocin in attenuating the abuse of licit and illicit drugs, including the psychostimulant methamphetamine, has been examined with increased ferocity in recent years. This is largely driven by the potential application of oxytocin as a pharmacotherapy. However, the neural mechanisms by which oxytocin modulates methamphetamine abuse are not well understood. Recent research identified an important role for the accumbens core and subthalamic nucleus in this process, which likely involves an interaction with dopamine, glutamate, GABA, and vasopressin. In addition to providing an overview of methamphetamine, the endogenous oxytocin system, and the effects of exogenous oxytocin on drug abuse, we propose a neural circuit through which exogenous oxytocin modulates methamphetamine abuse, focusing on its interaction with neurochemicals within the accumbens core and subthalamic nucleus. A growing understanding of exogenous oxytocin effects at a neurochemical and neurobiological level will assist in its evaluation as a pharmacotherapy for drug addiction.

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Methamphetamine (N-methyl-O-phenylisopropylamine; METH) is a commonly abused and highly addictive illicit drug. Globally, amphetamine-type stimulants were reported to have been used by 33.9 million individuals in 2013, making it the second most commonly used illicit drug type following cannabis (United Nations Office on Drugs and Crime, 2015). Usage rates in Australia are one of the highest worldwide, whereby 70% of regular drug users reported administering METH within the last 6 months, and 24% reported it was their drug of choice (Stafford and Burns, 2015). Particularly alarming is the increased preference for using crystalline methamphetamine, the highest purity form of the drug, in Europe, East and South-East Asia, as well as in Australia (Australian Institute of Health and Welfare, 2014; United Nations Office on Drugs and Crime, 2015). A recent Australia-wide survey reported that 50% of recent users preferred the crystalline form; an increase from 22% in 2010 (Australian Institute of Health and Welfare, 2014).

Regular misuse of METH is associated with a myriad of serious medical, cognitive, and psychosocial problems for the drug user, which are not only experienced whilst abusing the drug, but also following cessation of use. In addition to the hazardous impact of METH abuse on the individual, the estimated cost of METH abuse following cessation of use. In addition to the hazardous impact of METH abuse on the individual, the estimated cost of METH abuse is in the United States in 2005 alone was $23.4 billion, which included the costs associated with health care, hospital-based treatment, arrests, custodial care of children, and cleaning up of clandestine laboratory sites (RAND Drug Policy Research Center, 2009). Currently, there are no widely accepted effective pharmacotherapeutic treatments or psychosocial interventions to reduce METH abuse and dependence (Ciketic et al., 2012). The significant impact this drug has on both the user and the community highlights the need for the development of more effective pharmacological treatment strategies.

The neuropeptide oxytocin has been proposed as a potential pharmacological treatment for drug dependence. Exogenously administered oxytocin modulates the rewarding effects and abuse potential of numerous licit and illicit drugs including METH. However, the mechanisms of oxytocin action within the brain are not well understood, restricting awareness of the neurobiological implications of oxytocin treatment. Recent advancements have identified the nucleus accumbens (NAC) core and subthalamic nucleus (STh) as key regions involved in oxytocin modulation of methamphetamine-related reward and abuse (Baracz et al., 2012; Carson et al., 2010b). Further, oxytocin interacts with the neurotransmitters dopamine (DA), gamma aminobutyric acid (GABA), and glutamate, as well as the structurally similar neuropeptide arginine vasopressin (AVP) to modulate numerous functions. We will propose that oxytocin is acting within a circuit connecting these two brain regions to attenuate METH reward and abuse through an interaction with dopamine, glutamate, GABA, and AVP.

This review will initially provide an overview of METH pharmacology and the adverse effects associated with chronic administration in human populations. Following this, it will focus on the endogenous oxytocin system and existing literature on the impact of oxytocin administration on drug effects, with a particular focus on METH. An overview of the NAC core and STh will then be presented as well as the manner in which oxytocin interacts with the aforementioned neurotransmitters and AVP. Subsequently a circuit will be proposed which incorporates both brain regions and the mechanisms through which oxytocin could be interacting to modulate METH reward and abuse, and finally the applicability of oxytocin as a pharmacotherapy will be discussed.

2. Methamphetamine

2.1. Pharmacology

Methamphetamine is a synthetically produced cationic molecule, which is derived from the psychostimulant amphetamine (alpha-methyl-phenethyl-amine; (Zorick et al., 2008). Both molecules are similar in structure, although METH is more lipophilic, increasing its ability to cross the blood-brain barrier. This greatly increases its potency when compared to its parent compound (Rose and Grant, 2008; Zorick et al., 2008).

Methamphetamine can be snorted, smoked, injected or ingested (Elkashef et al., 2008). When injected, smoked or inhaled, the subjective effects of the drug are rapidly experienced within 10–20 min following administration (Cruickshank and Dyer, 2009). Oral administration results in substantially lower bioavailability and a slower peak in experiencing the subjective effects (45 min to 1.5 h; Rose and Grant, 2008). The subjective effects of METH have been reported to occur for approximately 8–12 h following administration, which is in keeping with the long 12-h half life of the drug (Meredith et al., 2005).

2.2. Mechanisms of action following acute administration

The highly addictive properties of METH are attributable to its effect on monoamine neurotransmission. Following administration, METH rapidly and sustainably increases the concentration of DA, serotonin and noradrenaline available in the synapses (Rothman et al., 2001; Zorick et al., 2008). As an inverse agonist, METH increases extracellular levels of the monoamines by three mechanisms: (i) reversal of the vesicular monoamine transporter-2, which results in the release of intravesicular monoamines from storage vesicles into the cytosol, (ii) reversal of the DA, serotonin and noradrenaline transporters, causing the release of the monoamines from the cytosol into synapses, and (iii) the inhibition of monoamine oxidase to impede metabolism of the available monoamines (Elkashef et al., 2008; Zorick et al., 2008). As METH reverses or inhibits mechanisms that regulate synaptic clearance of monoamines, a strong and sustained effect to increase the synaptic levels of these monoamines is produced.

2.3. Subjective, physiological, and cognitive effects of acute methamphetamine administration

The resultant increase in monoamine activity, coupled with stimulation of the sympathetic nervous system following acute METH administration is associated with various subjective, physiological, and cognitive effects. Typically, users describe experiencing a “rush” or “high”, which is characterised by euphoria,
increased energy, improved confidence and self-esteem, hypersexuality, reduced fatigue and appetite suppression (Elkashef et al., 2008; Zorick et al., 2008). Improvements in cognitive processing, such as increased sustained and divided attention, and improved reaction time can also be experienced following METH use, where it is often consumed to assist with engaging in tedious activities for extended periods of time (Cruickshank and Dyer, 2009; Looby and Earleywine, 2007).

Positive subjective effects are not always experienced by METH-naive individuals. By contrast, the hyper-excited state can result in anxiety and insomnia (Elkashef et al., 2008). Additionally, paranoia, aggression, depression, irritability, hallucinations, and delusions of parasitosis have been reported (Darke et al., 2008; Elkashef et al., 2008; Rose and Grant, 2008). Further, the physiological symptoms typically experienced following acute METH administration are adverse and include tachycardia, hypertension, tachypnoea, peripheral hyperthermia, dehydration, and diaphoresis (Donaldson and Goodchild, 2006; Rose and Grant, 2008; Zorick et al., 2008). To date, a distinction between the sexes of the acute experience of METH administration has not been reported.

2.4. Complications surrounding chronic methamphetamine use

2.4.1. Methamphetamine dependence

The prevalence of a lifetime stimulant use disorder is relatively high in Australia, with 3.3% of respondents on a national population based survey meeting DSM-IV diagnostic criteria (Sara et al., 2012). Of the 3.3% of respondents, 69% were male, which is in keeping with METH use reportedly being higher in males than in females (Australian Institute of Health and Welfare, 2014; Sara et al., 2012). Dependence on METH use is characterised by compulsive and uncontrolled administration despite the associated harms, tolerance, withdrawal, and typically relapse to compulsive drug taking (Darke et al., 2008; Rose and Grant, 2008). Tolerance to the acute effects of METH is often evident when users transition from less efficient routes of administration to more efficient routes (e.g. from oral administration to injecting), use more frequently, at higher doses, and greater purity (crystalline METH), in an attempt to re-experience the initial “high” (Darke et al., 2008). This change in METH use also typically reflects the degree of dependence on METH, whereby higher rates of dependence have been reported by users who predominantly use the crystalline form as well as principally smoke or inject METH (McKetin et al., 2006). Withdrawal from METH use is characterised by craving, depression, anxiety, anhedonia, fatigue, increased appetite, changes to sleep patterns and psychomotor slowing or agitation, where the severity of the withdrawal symptoms is dependent on the duration and frequency of METH use (Darke et al., 2008; Rawson, 2013). Typically, the more severe withdrawal symptoms last for approximately one to three weeks, although more subtle symptoms such as anhedonia can persist for several months to one year (McKetin et al., 2013a, 2013b; Rawson, 2013; Rose and Grant, 2008).

2.4.2. Overdose and neurotoxicity

The symptom presentation of a METH overdose can vary substantially and incorporates both physical and psychological symptoms. In terms of the medical problems, nausea, vomiting, profuse perspiration, tremors, shortness of breath, chest pain, heart palpitations, and seizures can be experienced (Darke et al., 2008; Hamamoto and Rhodus, 2008). Psychological symptoms that have been reported include agitation, high levels of anxiety, paranoia, hallucinations and suicidal ideation (Darke et al., 2008). Fatal METH overdoses commonly result from pulmonary oedema, pulmonary congestion, brain haemorrhage, ischaemic stroke, seizure, ventricular fibrillation, and acute cardiac, respiratory, or renal failure (Cruickshank and Dyer, 2009; Darke et al., 2008; Hamamoto and Rhodus, 2008).

Methamphetamine-induced neurotoxicity can occur due to the typically escalating doses that are administered as tolerance to the initial euphoric effects develops (Darke et al., 2008). Neurotoxic effects include the destruction of DA and serotonin axons and axon terminals, and reduced dopamine transporter (DAT), DA D2 receptor, serotonin transporter, and vesicular monoamine transporter densities (McCann and Ricaurte, 2004; Zorick et al., 2008). The decrease in monoamine transporter density is widespread, where DAT reductions are particularly prevalent in the orbitofrontal cortex, prefrontal cortex (PFC) and dorsal striatum (McCann et al., 2008; Sekine et al., 2003), whilst the reduction in serotonin transporters is most evident in the midbrain, dorsal striatum, hypothalamus, thalamus, and the orbitofrontal, temporal and cingulate cortices in METH-dependent users (Sekine et al., 2006).

Morphological studies have identified structural changes to the brain of METH users. A loss of grey matter in the cingulate, limbic and paralimbic cortices has been identified, as well as hippocampal shrinkage (Thompson et al., 2004). Globally, hyperintensities of white matter (Bae et al., 2006), decreases in the neuronal marker n-acetylaspartate (Sung et al., 2007), reductions in myoinositol, a marker for glial activation (Sung et al., 2007), and decreases in creatine, a marker of metabolic integrity (Sekine et al., 2002), are evident. The damage due to neurotoxicity persists following abstinence and is associated with cognitive, neurological and behavioural problems (McCann and Ricaurte, 2004). Violent behaviour is one such manifestation of the decline in serotonin transporter density (Zorick et al., 2008), whilst depletions of DA levels are associated with Parkinson’s disease symptoms, due to the common expression of psychomotor dysfunction and damage to DA neurons in the nigrostriatal pathway (Volkow et al., 2001).

2.4.3. Physical complications

Methamphetamine use is cardiotoxic as it places high demands on the cardiovascular system (Darke et al., 2008). Repeated METH administration can result in acute coronary syndrome, myocardial ischaemia, and in some cases myocardial infarction, atrial and ventricular dysrhythmias, cardiovascular collapse, cardiomyopathy, pulmonary hypertension, and coronary heart disease (Turnipseed et al., 2003). Methamphetamine-dependent individuals are also at a higher risk of experiencing an haemorrhagic or ischaemic stroke (Westover et al., 2007).

The use of METH during pregnancy is associated with a myriad of difficulties and defects that can become apparent in utero and later in life. During early gestation, METH exposure can have substantial teratogenic effects on the foetus (Behnke and Smith, 2013). In addition, METH use in pregnant women has also been associated with loss of the foetus, premature birth, low birth weight, and with heavier use, neonatal withdrawal syndrome (Linden et al., 2013). Difficulties can also be evident at an older age, where children can have difficulties with learning and memory, behavioural problems, and be intellectually impaired (Linden et al., 2013).

Dental deterioration often results from chronic METH abuse. Commonly termed “meth mouth”, the symptoms include blackened, rotting, or crumbling teeth, as well as xerostomia or dry mouth, bruising and muscle trismus, or reduced opening of the jaw (Hamamoto and Rhodus, 2008; Shetty et al., 2010). This combination of symptoms typically occurs due to poor oral hygiene, high intake of sugary beverages and refined carbohydrates, increased acidity in the mouth from orally consuming METH, accumulation of chemical residue from smoking METH, as well as vomiting following METH administration (Hamamoto and Rhodus, 2008).

Additional problems from chronic METH use can arise due to higher-risk routes of administration. Intravenous injection of
METH is associated with higher rates of blood-borne viruses. Such diseases include human immunodeficiency virus (HIV) and Hepatitis A, B, and C (Hamamoto and Rhodus, 2008). Poor needle hygiene can additionally result in endocarditis and pulmonary abscess (Richards et al., 1999). Smoking METH regularly is related to a number of respiratory problems including bronchitis, pulmonary oedema, haemoptysis, and granuloma.

2.4.4. Psychiatric symptoms

Psychopathology is typically experienced by both METH-dependent individuals and those withdrawing from METH use. Symptoms of depression and anxiety are particularly common in this group, and have been reported when regularly using METH and at higher rates during abstinence (Looby and Earleywine, 2007; Darke et al., 2008; Rose and Grant, 2008). In keeping with this, high rates of self-harm, suicidal ideation, and suicide attempts are reported in METH users, whereby approximately a quarter of METH users will attempt suicide at some point in their lifetime (Dyer and Cruickshank, 2007). Both rates of depression and suicidal behaviour are reported to be experienced more commonly by women using METH than by men (Dluzen and Liu, 2008).

It has been well documented that psychostimulant administration can induce psychosis and that this can be experienced whilst regularly using METH or during periods of abstinence. The symptoms experienced are typically indistinguishable from schizophrenia, and include auditory and visual hallucinations, as well as delusions of reference and persecution (Harris and Batki, 2000). Psychosis is usually transiently experienced, however, in severe cases, psychotic symptoms can persist for a week following abstinence (McKetin et al., 2013b). Psychotic symptoms can be experienced by METH users who have no family history of a psychotic or schizophrenic illness (McKetin et al., 2005). In those with a family history, METH use can precipitate a schizophrenic episode, or in those who have already been diagnosed with schizophrenia, can exacerbate their symptoms (Harris and Batki, 2000). Further, psychotic symptoms can be triggered by stress in formally psychotic METH users who are now abstinent, which makes correct psychiatric diagnosis substantially more difficult (Harris and Batki, 2000).

2.4.5. Cognitive deficits

In contrast to the improvements in cognitive functioning which can be experienced when administered acutely at low to moderate doses, cognitive deficits have been reported with repeated METH use and following abstinence. Difficulties with learning, memory, sustaining attention, and decision-making have been identified, as well as slowed processing of information (Cruickshank and Dyer, 2009; Dean et al., 2013; Meredith et al., 2005; Ornstein et al., 2000). Such cognitive decline is consistent with damage to the frontalstrial and limbic brain areas (Ornstein et al., 2000). Furthermore, a discrepancy in performance on tasks of cognitive ability have been identified between men and women who are currently using METH, whereby men are reported to perform worse than women on tasks of executive functioning and auditory verbal learning (Dluzen and Liu, 2008).

In abstinence users, problems with cognition can persist, with continued difficulties in memory, learning, and executive and motor function (Herbeck and Brecht, 2013; McCann and Ricaurte, 2004). Although the presence and degree of cognitive deficits varies amongst METH users and those who are abstinence, greater difficulties are typically reported by those who had pre-existing cognitive difficulties, are poly-drug users, or are those experiencing psychiatric symptoms (Herbeck and Brecht, 2013; McCann and Ricaurte, 2004).

The high worldwide prevalence of METH usage coupled with the myriad of adverse effects that are associated with repeat administration of METH highlight the need for effective pharmacotherapies. Whilst psychotherapy such as cognitive behavioural therapy and contingency management typically have positive outcomes during treatment, they are expensive, have poor retention rates and a greater than 50% rate of relapse 6–19 months following treatment completion (Ciketic et al., 2012; Courtney and Ray, 2014; Ling et al., 2014). Similarly, residential rehabilitation facilities reportedly have relapse rates greater than 60% at 1–2 year follow up in both America (Brecht and Herbeck, 2014) and Australia (McKetin et al., 2012). Furthermore, numerous classes of pharmacological agents such as monoamine agonists (fluoxetine), DA agonists (bupropion, dexamphetamine), DA antagonists (haloperidol) and GABA receptor agonists (baclofen) have been investigated in clinical trials for their pharmacotherapeutic potential, however, they have failed to receive approval from the Food and Drugs Administration (FDA) or Therapeutic Goods Administration (TGA; the Australian equivalent of the FDA) for treating METH dependence (Ciketic et al., 2012). Considering the limited effectiveness of the more traditional pharmacological treatments, alternative pharmacotherapies that may indirectly modulate METH effects, such as oxytocin, are being investigated as potential treatment options for drug dependence.

3. Oxytocin

3.1. Synthesis and release

Oxytocin is a nine-amino acid neuropeptide (Pow and Morris, 1989). This compound is primarily synthesised in the central nervous system by the magnocellular neurons located within the paraventricular nucleus (PVN), supraoptic nucleus (SON), and accessory nucleus of the hypothalamus (Pow and Morris, 1989; Swanson and Sawchenko, 1983). The magnocellular neurons project to the posterior pituitary where oxytocin is released into the general blood stream to act as a hormone on peripheral targets (Bargmann and Scharrer, 1951; Brownstein et al., 1980). Additionally, oxytocin is released from magnocellular neurons within the SON and PVN to act on oxytocin receptors (OTR) that are distributed widely throughout the brain (Landgraf and Neumann, 2004; Ludwig and Leng, 2006; Pow and Morris, 1989). Ascending oxytocinergic pathways largely originate from the PVN to innervate limbic and forebrain regions as well as substrates of the basal ganglia and midbrain (Dolen et al., 2013; Fuxe et al., 2012; Gimpl and Fahrenholz, 2001). Oxytocinergic fibres from the SON project to limited forebrain regions namely the NAC, central amygdala, lateral septum, CA1 of the hippocampus, and the horizontal limb of the diagonal band of Broca (Knobloch et al., 2012). The descending oxytocin pathway originate in the parvocellular neurons of the PVN, where less oxytocin is synthesised, and projects to the autonomic regions of the lower brain stem, medulla and pons (Fuxe et al., 2012; Lee et al., 2009; Pinol et al., 2012).

In addition to oxytocin acting as a neurotransmitter through fast synaptic signalling along wired axonal pathways, it also acts as a neuromodulator through volume transmission. This is achieved through non-synaptic release from either the dendrites or soma of the neuronal membrane to regulate its own activity (Moos et al., 1984) and target distant brain regions (Landgraf and Neumann, 2004; Ludwig and Leng, 2006; Neumann, 2007). It has long been thought that oxytocin largely released from the SON is diffusely transmitted throughout the brain, and with a half-life of 20 min and no spatial restriction to synapses, its release can affect distal brain regions (Landgraf and Neumann, 2004; Ludwig and Leng, 2006; McGregor et al., 2008; Neumann, 2007). However, recent technological advances have furthered understanding of non-synaptic release, indicating that a combination of focal and non-synaptic release can produce fast behavioural, emotional,
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<td>Repeated morphine administration</td>
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<td>Cocaine</td>
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<td>Cocaine</td>
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<td>Methamphetamine</td>
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<td>Pair housed, chronic methamphetamine exposure</td>
<td>Intracranial</td>
<td>Decreased acquisition of CPP Decreased drug-primed reinstatement</td>
<td>Baracz et al. (2012) Baracz et al. (2015, 2016a)</td>
</tr>
<tr>
<td>Methamphetamine</td>
<td>Rat</td>
<td>Female</td>
<td>Chronic methamphetamine exposure</td>
<td>Intraperitoneal</td>
<td>Decreased motivation to self-administer and decreased drug-primed reinstatement when administered during adolescence</td>
<td>Hicks et al. (2016)</td>
</tr>
</tbody>
</table>
and cognitive responses. Knobloch et al. (2012) elegantly showed that oxytocinergic fibres projecting from the dorsolateral accessory nuclei of the hypothalamus to the lateral division of the central amygdala focally release oxytocin through diffuse transmission within a short 100-μm distance. At present, it appears that oxytocin can communicate in a fast point-to-point manner through synaptic and non-synaptic signalling, as well as through slow and global release as a neuromodulator to have longer lasting effects.

3.2. The oxytocin receptor

At the present time, one OTR has been identified, which is a member of the rhodopsin-type class I G-protein coupled receptor family (Gimpl and Fahrenholz, 2001). This oxytocin receptor can be functionally coupled to G0, Gα, and Gi proteins to activate various intracellular signalling pathways. Coupling with the Gα protein activates phospholipase C, which subsequently increases intracellular Ca2+ ions and protein kinases type C, Gi coupling activates adenylyl cyclase and stimulates cyclic adenosine monophosphate (cAMP) production, and coupling with Gi inhibits cAMP production (Gimpl and Fahrenholz, 2001; Strunecka et al., 2009; Viero et al., 2010). As such, various intracellular signalling pathways can be activated through the coupling of the OTR to different G proteins to produce different behavioural outcomes.

The OTR is extensively distributed throughout the brain in a species dependent manner. In the rat, the OTR has been abundantly located in the basal ganglia, limbic system, peduncular cortex, thalamus, hypothalamus, olfactory system, brain stem and spinal cord (Adan et al., 1995; Gimpl and Fahrenholz, 2001). Sex differences in OTR expression have also been described (for review see Dumais and Veenema, 2016). Mapping of the OTR in the human brain is a relatively recent endeavour. Currently, the OTR has been located in cortical, hypothalamic and limbic regions, showing a modest overlap with OTR localisation in the rat brain (Boccia et al., 2013). Altogether, the widespread localisation of the OTR, the focal and global transmission of oxytocin, and the diverse intracellular signalling pathways that can be activated highlight that oxytocin can modulate a wide range of behaviours.

3.3. Effect on behaviour

Commonly termed the social neuuropeptide, oxytocin is involved in the modulation of numerous social, emotional, and sexual behaviours, in addition to its classical peripheral effects on uterine contractions during parturition and milk letdown during lactation (Dawood et al., 1981). Oxytocin promotes maternal behaviour, sexual arousal, erectile function and ejaculation, social interaction, the formation of mother-infant and monogamous pair bonds, and can enhance trust in humans (Hollander et al., 2007; Lee et al., 2009; McGregor et al., 2008; Young et al., 2001). Further, oxytocin has anxiolytic and antidepressant properties, and reduces stress responses by attenuating the hypothalamic-pituitary-adrenal axis (Bülbül et al., 2011; Neumann and Landgraf, 2012).

The abuse of drugs is strongly associated with social context, where the initiation of drug use can be influenced by social groups or settings, and can result in numerous social consequences when taken acutely or chronically. In keeping with this, the regulation of the endogenous oxytocin system has been associated with resilience to addiction in humans (Buismann-Pijlman et al., 2014) and exogenously administered oxytocin has been associated with modulating licit and illicit drug-related behaviours in animals (Sarnyai and Kovacs, 2014; see Table 1). Rodent studies, largely conducted using males, have demonstrated that systemic or central injections of oxytocin decreased the self-administration of heroin in heroin-tolerant rats (Kovacs et al., 1985a), reduced the development of tolerance to, and physical dependence on morphine (Kovacs et al., 1985b, 1986), and decreased cannabinoid withdrawal symptoms (Cui et al., 2001). Systemic oxytocin administration has also been shown to attenuate cocaine-induced stereotypy (Sarnyai et al., 1991), tolerance (Sarnyai et al., 1992), and drug-primed reinstatement to cocaine seeking in male rats, and cocaine-induced locomotion (Kovacs et al., 1990; Leong et al., 2016; Zhou et al., 2014), cocaine intravenous self-administration, and cue-induced reinstatement in male and female rats (Leong et al., 2016; Sarnyai and Kovacs, 1994; Zhou et al., 2014). Both peripheral and central administration of oxytocin reduced preference and consumption of alcohol in male and female alcohol preferring rats (McGregor and Bowen, 2012) and in a standard rat strain (Macfayden et al., 2016) as well as reducing tolerance to alcohol in mice (Szabo et al., 1989). Oxytocin pre-treatment during adolescence can also have long lasting effects on alcohol consumption in adulthood, whereby 10 days of oxytocin pretreatment in a standard rat strain attenuated alcohol consumption in adulthood (Bowen et al., 2011).

Preliminary clinical trials with intranasal oxytocin in a population of drug users have so far identified largely positive findings. Presently, clinical trials examining alcohol, marijuana, and cocaine-dependent humans of either sex suggest that acute intranasal administration of oxytocin reduced alcohol withdrawal symptoms (Pedersen et al., 2012), marijuana craving following exposure to a psychosocial stressor (McRae-Clark et al., 2013), and the association between cocaine-related cues and state anger, a factor that can encourage drug taking behaviour (Lee et al., 2014). However, acute oxytocin administration has also been associated with null or worsening effects, whereby opioid dependent males receiving opioid replacement therapy (ORT) did not experience a reduction in cue-induced craving or heroin-related implicit associations, and performed worse on social perception tasks following oxytocin administration (Woolley et al., 2016). To date, one clinical trial has examined the effect of repeated intranasal oxytocin administration in drug-dependent individuals (Stauffer et al., 2016). Twice daily oxytocin administration for two-weeks by cocaine users who were receiving ORT for their heroin dependence reduced cocaine craving, stabilised heroin craving, which increased in controls, promoted a transition to associating drug use with others rather than the self, and elicited a trend in reducing self-reported cocaine use.

The examination of oxytocin modulation of METH-related behaviours was initiated much more recently and again primarily using male rodents. Acute intracerebroventricular (icv) oxytocin administration was shown to reduce METH-induced hyperactivity in mice (Qi et al., 2008). Oxytocin administration also modulates reward processes (although see Subiah et al., 2012), whereby icv oxytocin injections in mice attenuated the acquisition of a conditioned place preference (CPP) for METH and blocked stress induced relapse to METH-seeking behaviour (Qi et al., 2009). Further, systemic injections of oxytocin reduced the self-administration of METH in rodents, as well as reinstatement to METH-seeking behaviour when exposed to a drug prime (Carson et al., 2010a). Oxytocin pretreatment during adolescence has also been shown to modulate addiction-related behaviours in adulthood, whereby it reduced lever press responding for METH under a progressive ratio schedule of reinforcement as well as during METH-primed reinstatement in adult female rats (Hicks et al., 2016). Interestingly, in a study comparing oxytocin modulation of METH abuse in male and female rats, systemic oxytocin administration reduced the self-administration of METH and cue-induced reinstatement in...
female rats only, and attenuated drug- and stress-induced reinstatement in both sexes (Cox et al., 2013), highlighting the necessity for examining sex differences in oxytocin-mediated effects. Altogether, the current literature suggests that oxytocin administration can affect addiction-related behaviours when injected prior to, as well as following, acute and chronic drug administration.

4. Brain regions involved in oxytocin and methamphetamine interactions

Recent investigations have furthered our understanding of the neurobiological substrates involved in oxytocin modulation of acute METH exposure. Carson et al. (2010b) demonstrated that peripherally administered oxytocin, an acute METH injection reduced METH-induced c-Fos expression in the NAc core and the STh, in addition to METH hyperactivity. Such findings indicate that both regions are critically involved in oxytocin reduction of acute METH-related effects.

4.1. Nucleus accumbens core

The NAc is considered a key neural substrate involved in reward and motivation (Bjorklund et al., 2008; Ito et al., 2004; Sellings and Clarke, 2003). This brain region makes up the ventral component of the striatum and is the terminal region of the mesocorticolimbic reward pathway (Carlezon and Thomas, 2009). The NAc receives glutamatergic input from the PFC, the hippocampus, and amygdala, and dopaminergic input from the ventral tegmental area (Joffe et al., 2014; Koch et al., 2000). In terms of output, the NAc is divided into two subregions, the medioventral shell and the dorsal-lateral core, both of which project to independent brain regions (Usada et al., 1998). The medioventral shell projects to the medial ventral pallidum, lateral hypothalamus, ventral tegmental area, substantia nigra pars reticulata, and the extended amygdala (Joffe et al., 2014; Tripathi et al., 2010; Usada et al., 1998). Projections from the core subregion extend to the dorsal portion of the ventral pallidum, medial globus pallidus, substantia nigra pars compacta and SThs (Joffe et al., 2014; Tripathi et al., 2010; Usada et al., 1998).

The NAc is largely involved in the initial stages of drug addiction (Bjorklund et al., 2008). Following acute psychostimulant administration, increased DA is released in this brain region, which instigates the behavioural expression and pleasure associated with reward (Broom and Yamamoto, 2005; Di Chiara, 2002; Sellings and Clarke, 2003). Behaviourally, this has been shown by the direct self-administration of amphetamine into the NAC (Carlezon and Thomas, 2009). In addition, DA release in the NAC is associated with exposure to environments and cues which are related to drug administration (Ito et al., 2000).

The two subregions of the NAc are involved in different aspects of drug-related reward (Di Chiara, 2002; Ito et al., 2004). The shell subregion has been associated with the acute euphoric effects of psychostimulants (Broom and Yamamoto, 2005; Di Chiara, 2002; Ito et al., 2004). Acute METH administration increases DA release specifically within the NAc shell (Broom and Yamamoto, 2005), and lesions to the shell subregion attenuate the psychostimulant effects of cocaine (Ito et al., 2004). More recently, the shell subregion has also been associated with modulating valence, whereby the rostral area of the medial shell is involved in appetitive behaviours, and caudal sites are integral for fear generation (Reynolds and Berridge, 2008). The core subregion, alternatively, is associated with behavioural responses to environmental cues and stimuli that have motivationally significant outcomes (Di Chiara, 2002; Ito et al., 2004). Bilateral lesions to the core disrupt conditioned reinforcement between cues and the drug, such that cocaine-seeking behaviour decreased in core-lesioned rats (Ito et al., 2004). Moreover, direct application of the DA receptor antagonist flupenthixol attenuated cue-evoked cocaine seeking in rats experienced at cocaine self-administration, whilst a microinjection of amphetamine facilitated cocaine-seeking behaviour (Saunders et al., 2013). This highlights the involvement of the core subregion on behavioural outcomes to motivationally salient stimuli.

4.2. Subthalamic nucleus

The STh has traditionally been considered a key substrate involved in modulating motor behaviour and its dysfunction. Relatively recent research has identified that it also plays a crucial role in motivational aspects of both natural and drug reward. The STh is a small nucleus located within the basal ganglia (Parent and Hazrati, 1995). It is ventral to the zona incerta and dorsal to the cerebral peduncle (Nambu et al., 2002). The STh is an input structure, which uniquely is the sole basal ganglia nucleus to have glutamatergic neurons and an excitatory input on its target brain structures (Parent and Hazrati, 1995; Wilson and Bevan, 2011). The STh receives glutamatergic input from the cortex, GABAergic projections from the globus pallidus and ventral pallidum, and dopaminergic input from the midbrain (Hassani et al., 1997; Lardeux et al., 2009; Wilson and Bevan, 2011). It largely projects to the internal segment of the globus pallidus (GPI) and substantia nigra pars reticulata (SNr); the output nuclei of the basal ganglia (Lintas et al., 2012). To a lesser extent, STh neurons also project to the amygdala, striatum and substantia nigra pars compacta (Hassani et al., 1997).

Investigations exploring the inactivation of the STh were the first to recognise its involvement in modulating motivation for natural and drug reward. Bilateral lesions to the STh or high frequency stimulation increased motivation for food, whilst decreasing motivation for intravenous infusions of cocaine (Baunez et al., 2005; Rouand et al., 2010; Uslaner et al., 2005). The role of the STh on motivation increased in complexity when Lardeux and Baunez (2008) identified that preference for alcohol differentially affected motivation following bilateral lesions to the STh. Specifically, motivation for alcohol increased in rats who preferred alcohol, and decreased in rats exhibiting a low preference. Stimulation of the STh in humans using deep brain stimulation (DBS) has also shown reductions in pathological gambling in individuals with Parkinson's disease (Ardouin et al., 2006; Bandini et al., 2007) and addiction to their L-Dopa medication (Witjas et al., 2005) and has been proposed as a potential treatment for addiction (Pelloux and Baunez, 2013).

The STh is also associated with cues predicting rewarding outcomes. Specifically, the STh is involved in coding reward-related predictions and reward magnitude (Darbaky et al., 2005; Lardeux et al., 2009). Further, independent neuronal populations in the STh code for different concentrations of sucrose (Lardeux et al., 2009) as well as encode reward value for sucrose or cocaine (Lardeux et al., 2013). Considering that DA is associated with coding reward-related properties, it seems likely that STh neurons associated with reward value and magnitude are modulated by midbrain dopaminergic projections (Hassani et al., 1997; Lardeux et al., 2009).

4.3. Recent investigations on oxytocin modulation of the nucleus accumbens core and subthalamic nucleus on methamphetamine-related behaviours

Until recently, oxytocin modulation of drug-related reward and associated behaviours within the NAc was minimally investigated.
Seminal research from Kovacs laboratory reported that oxytocin microinjected into the NAc reduced intravenous self-administration of heroin in heroin-tolerant rats (Ibragimov et al., 1987) and reduced cocaine-induced stereotyped sniffing behaviour (Sarnyai et al., 1991). In contrast, the ability of oxytocin to attenuate drug-related effects within the STh had not been investigated prior to Carson’s et al. (2010b) study. Following on from Carson’s et al. (2010b) investigation, we further explored the involvement of the core region of the NAc and the STh in oxytocin modulation of acute METH reward (Baracz et al., 2012). Oxytocin microinjected into the NAc core or the STh attenuated the formation of a place preference to the METH-associated context. In addition, we went on to show that both regions are also involved in oxytocin modulation of METH-primed relapse in rats previously experienced at intravenous METH self-administration whereby local administration of oxytocin into the NAc core or STh attenuated reinstatement to METH-seeking behaviour (Baracz et al., 2015, 2016a).

The central mechanisms by which oxytocin administration attenuates METH-related behaviours remains relatively unknown. In our investigation of oxytocin attenuation of METH-seeking behaviour at the NAc core or STh (Baracz et al., 2015, 2016a), we examined if this effect was driven by the oxytocin system. The co-administration of desGly-NH₂,d(CH₂)₅[D-Tyr²,Thr⁴]OVT, the examined if this effect was driven by the oxytocin system. The co-administration of desGly-NH₂,d(CH₂)₅[D-Tyr²,Thr⁴]OVT, the most selective OTR antagonist currently available (Manning et al., 2012), with oxytocin in the NAc core or STh did not specifically block the modulating effect of oxytocin on METH lever pressing activity. However, we had previously demonstrated that oxytocin modulates acute dopamine reward in the STh through the OTR (Baracz and Cornish, 2013), suggesting that the importance of the OTR in regulating drug-related behaviours diminishes following chronic METH exposure. Indeed, we have shown a reduction in OTR-immunoreactive (ir) fibre density in the NAc core following 20 days of METH self-administration, when compared to rats that were yoked to receive saline infusions (Baracz et al., 2016b). Whilst a similar change to STh OTR-ir was not shown at this time point, following 15 days of extinction from METH self-administration, OTR fibre density in the anterior STh was augmented. In addition, following extinction a trend towards normalization of OTR-ir fibre density in the NAc core was evident compared to yoked controls, and rats that self-administered METH whom were not exposed to extinction conditions. These findings suggest that METH exposure can alter OTR-ir and that in the absence of chronic METH administration, a partial recovery of the oxytocin system in the NAc core occurred, together with a modulatory change to OTR-ir in the STh.

In agreement with our findings, Cadet et al. (2014) reported an increase in oxytocin mRNA in the NAc following repeated METH injections, consistent with a compensatory decrease in the OTR. In contrast, other groups have shown an upregulation of the OTR in brain regions other than the NAc core and STh, following repeated psychostimulant administration (Georgiou et al., 2015, 2016; Zanos et al., 2014). Regardless of the discrepant findings, which may be explained by differing methodologies including: the application of immunohistochemistry or receptor autoradiography, short or long periods of METH exposure and active or passive drug administration, the aforementioned studies all suggest that the OTR becomes dysregulated following chronic psychostimulant exposure. The change to the OTR may explain why we have shown that oxytocin has little effect through its own receptor in the NAc core and STh to modulate METH-primed reinstatement following chronic METH exposure (Baracz et al., 2015, 2016a) and may suggest that exogenously administered oxytocin may interact with other neurotransmitters or neuropeptides in these brain regions to modulate behaviours associated with chronic METH abuse.

5. Oxytocin interactions

5.1. Oxytocin and dopamine

Investigation into the manner in which oxytocin modulates socio-affiliative behaviours and drug reward within the brain has largely focused on its interaction with the catecholaminergic neurotransmitter DA. Oxytocin and DA receptors and neuronal fibres are largely located within the same brain regions and are in close apposition. Expression of the oxytocin and dopamine D₂ receptor overlap in the dorsal and ventral striatum (Fuxe et al., 2012); brain regions where D₂ receptor–OTR heteromers are also located (Romero-Fernandez et al., 2013). Dopamine receptors have also been located on oxytocin neurons, whereby D₂ and D₃ receptors have been identified on the cell bodies and dendrites of magnocellular and parvocellular oxytocin neurons of the hypothalamus, and D₃ receptors have been located exclusively on magnocellular oxytocin neurons in the PVN. In terms of fibre innervation, dopaminergic fibres from the incertohypothalamic system and ventral tegmental area extend to oxytocin nuclei in the hypothalamus, hippocampus and amygdala (Baskerville et al., 2009) and oxytocinergic fibres innervate mesocorticolimbic DA cell bodies in the ventral tegmental area that then terminate in the NAc (Baskerville and Douglas, 2010). The manner in which oxytocin and DA interact to influence behavioural outcomes is quite complex and appears to be dependent on both the behaviour (Baskerville and Douglas, 2010) and the brain region involved (Kovacs et al., 1990). Pair bond formation in female voles requires the concurrent activation of both oxytocin and D₂ receptors at the level of the NAc (Liu and Wang, 2003; Young et al., 2001). The initiation and maintenance of maternal behaviour, however, is driven by oxytocin through the modulation of DA release in the mesocorticolimbic circuit (Numan and Stolzenberg, 2009) (Shahrokh et al., 2010). In contrast, sexual behaviour in male rats appears to be driven by DA, whereby DA activates select oxytocin neurons depending on the context in which penile erection occurs (Baskerville et al., 2009; Baskerville and Douglas, 2010).

Unlike investigations into the oxytocin-DA interaction in socio-affiliative behaviours, behavioural pharmacology studies examining this interaction in drug reward and abuse are limited. It has been postulated that oxytocin administration attenuates the increased DA neurotransmission typically experienced following psychostimulant administration within the mesocorticolimbic circuit (McGregor et al., 2008; Qi et al., 2009, 2008). As oxytocin neuronal fibres have been located in apposition to DA cell bodies in the ventral tegmental area and innervate the PFC, which also receives dopaminergic input, this provides an anatomical foundation for hypothalamic oxytocin input into the mesocorticolimbic DA system (Baskerville and Douglas, 2010). Indeed, central or peripheral administration of oxytocin reduced the increased utilisation of DA in the NAc following cocaine administration (Kovacs et al., 1990) and in both the dorsal and ventral striatum following METH administration in male rodents (Qi et al., 2008). In a recent study, oxytocin microinjected into the prelimbic cortex reduced the increase in NAc DA levels produced by repeated amphetamine injections, which rescued amphetamine-induced impairments in the formation of pair bonds in female prairie voles (Young et al., 2014).

We have also investigated the interaction between oxytocin and DA within the STh on drug reward. We demonstrated that DA microinjected into the STh resulted in the formation of a conditioned place preference for DA, which was attenuated by the co-administration of oxytocin (Baracz and Cornish, 2013). Moreover, when a cocktail of DA, oxytocin and the highly selective OTR.
antagonist desGly-NH$_2$d(CH$_2$)$_3$[D-Tyr$^2$, Thr$^8$]OVT was directly administered into this brain region, desGly-NH$_2$d(CH$_2$)$_3$[D-Tyr$^2$, Thr$^8$]OVT blocked the inhibiting effect of oxytocin on place preference formation. Considering that DA is a primary neurotransmitter involved in reward processes (Hyman et al., 2006; Koob, 2009; Schultz, 2000) and is largely implicated in METH-related reward (Schultz, 2000), the findings postulate that within the STh, oxytocin likely attenuates METH reward by reducing DA activity through activation of the OTR. However, when considering chronic psychostimulant abuse and addiction, DA is not the only neurotransmitter involved, nor is it the only neurochemical that oxytocin interacts with to modulate behaviour.

5.2. Oxytocin and arginine vasopressin

Oxytocin and AVP are structurally similar neuropeptides. In terms of their chemical structure, they only differ by two amino acids at positions 3 and 8, and the genes for the neuropeptides, which are highly homogenous, share the same chromosomal locus, although are transcribed in opposite directions (Gimpl and Fahrenholz, 2001; Lee et al., 2009). In accordance, the OTR and AVP receptors show high sequence homology, providing a structural reason for the ability of oxytocin to bind to AVP receptors, albeit at a slightly lower affinity than the OTR (Chini and Manning, 2007; Tribollet et al., 1988). Considering this, it is possible that oxytocin is binding to AVP receptors to modulate relapse to METH-seeking behaviour.

Like the OTR, AVP receptors are G-protein coupled (Chini and Manning, 2007). Currently, three AVP receptors have been identified; the V1a, V1b, and V2 receptors. The V2 receptor has been located almost solely within the kidneys, whilst V1a receptors have been identified both peripherally as well as centrally within the brain, with the V1a receptor being the most widely expressed (Hernando et al., 2001; Stoop, 2012). The distribution pattern of AVP V1 receptors largely differs to the OTR and where both neuropeptide receptors are located in the same brain region, they are typically expressed in different subsections (Gimpl and Fahrenholz, 2001; Tribollet et al., 1992). The hippocampus provides a prime example, where the OTR has been located in the subiculum, whilst AVP V1 receptors have been identified in the CA1 area as well as the inner and outer segments of the dentate gyrus (Tribollet et al., 1992). Altogether, it is not surprising that oxytocin and AVP are both involved in numerous social behaviours and in modulating anxiety, although typically having opposing effects. Oxytocin generally has prosocial effects, facilitates prosocial and autonomic effects that were previously attributed to the OTR, oxytocin acts through the V1a receptor to modulate numerous social and autonomic actions in male rodents. Considering these findings, together with our discovery of the non-specific effect of OTR antagonism on oxytocin modulation of METH-seeking behaviour in the NAc core (Baracz et al., 2016a) and STh (Baracz et al., 2015), we are currently investigating the involvement of the V1a receptor in METH IVSA through the co-administration of oxytocin and SR49059. Consistent with the literature, our preliminary findings show that systemic administration of SR49059 blocks the oxytocin-induced reduction in relapse to METH-seeking behaviour (unpublished data), providing important insight into one of the potential mechanisms by which oxytocin could be modulating METH-related behaviours in the NAc core and STh.

5.3. Oxytocin and amino acids

The amino acids glutamate and GABA are also involved in acute psychostimulant effects as well as drug dependence and craving through the dysregulation of their respective systems (Cornish and Kalivas, 2000; Kalivas and Volkow, 2011). Although not as extensively investigated as its interaction with dopamine or AVP, oxytocin interacts with both glutamate and GABA to modulate a range of behaviours. More specifically, GABAergic projections to the supraoptic nucleus innerne oxytocin neurons (Theodosius et al., 1986) and inhibit oxytocin neuronal electrical and secretory activity when under social defeat stress (Engelmann et al., 2004). Intracerebroventricular administration of oxytocin prior to an ethanol injection has also been shown to attenuate ethanol-induced motor impairment as well as increased GABAergic activity through activating δ-GABA-A receptors (Bowen et al., 2015). When exposed to forced swim conditions, oxytocin release in the central amygdala of female rats inhibits glutamate release to modulate stress responses (Bosch et al., 2007). Further, intrathecal oxytocin administration in the dorsal horn of the spinal cord blocks glutamate-mediated sensory transmission in cold swim and restraint-stress induced antinociception (Robinson et al., 2002).

An interaction of oxytocin with glutamate and GABA in METH-related behaviours has also been investigated specifically in the medial PFC and dorsal hippocampus. Qi et al. (2012) demonstrated that icv administration of oxytocin prior to an acute METH injection inhibited the METH-induced reduction in extracellular GABA levels in the dorsal hippocampus, whilst in the medial PFC oxytocin administration stimulated an increase in baseline extracellular GABA levels, as well as inhibited the METH-induced increase in glutamate levels. The same research group also demonstrated, using the reinstatement model of CPP, that central oxytocin administration inhibits restraint stress-induced reinstatement to METH-seeking behaviour partially by inhibiting stress-induced increases in extracellular glutamate levels in the medial PFC (Qi et al., 2009).

It is plausible that oxytocin also interacts with these amino acids in the NAc or the STh to modulate METH-related behaviours. The NAc receives glutamatergic input from numerous brain regions (Ikeda et al., 2012), is largely composed of GABAergic medium spiny neurons (Liang et al., 2014), and consists of metabotropic (mGluR5) and ionotropic (AMPA and NMDA) glutamate receptors, and GABA-A and -B receptors (Ikeda et al., 2012; Liang et al., 2014; Roohi et al., 2014). Similarly, glutamatergic and GABAergic fibres project to the STh (Wilson and Bevan, 2011).
and both GABA-A and -B receptors and metabotropic (mGluR1 and mGluR5) glutamate receptors have been located in this brain region (Boyes and Bolam, 2007; Marino et al., 2002). Further, as DA typically modulates GABA and glutamate neurotransmission (Beaulieu and Gainetdinov, 2011), it is possible that a complex process is involved in oxytocin modulation of METH-related reward and particularly relapse to METH-seeking behaviour that incorporates an interaction of DA with GABA and glutamate regulation of the NAc core and STh.

6. Integrating oxytocin activity at the NAc core and STh in drug addiction circuitry

Carson et al. (2010b) demonstrated in their pivotal study that oxytocin attenuated acute METH-induced cellular activation only within the NAc core and STh. This suggests that the NAc core and STh may be closely linked in oxytocin modulation of acute METH processes. Indeed, one of the many multi-synaptic circuits that connect the cerebral cortex with the output nuclei of the basal ganglia has projections from the NAc core through to the STh (see Fig. 1; Maurice et al., 1998). This indirect cortico-striato-pallido-subthalamic circuit incorporates projections from the medial PFC to the NAc core, which then project to the ventral pallidum and finally to the medial STh. The STh influences the activity of the internal segment of the globus pallidus (GPI) and substantia nigra pars reticulata (SNr); the output nuclei of the basal ganglia (Maurice et al., 1998). Activation of the indirect circuit results in late or slower disinhibition of the STh (Kolomiets et al., 2001). Specifically, stimulation of the medial PFC glutamate projections to the NAc core activates GABAergic projections to ventral pallidal GABA cells, leading to a disinhibition of cells within the STh (Maurice et al., 1998). An additional hyperdirect pathway incorporating glutamatergic input to the STh from the medial PFC provides early or immediate excitation of the STh. As STh neurons are glutamatergic, excitation of these neurons through either the hyperdirect or indirect pathway increases activity of the GPI and SNr. Neuronal fibres of the output nuclei are GABAergic, where their excitation has an inhibitory effect on thalamo-cortical circuits to initiate behaviour. Ultimately, activation of the STh is thought to suppress any inappropriate or maladaptive behaviours through activating the inhibitory fibres of the output nuclei of the basal ganglia (Hamani et al., 2003; Shen et al., 2003; Smith et al., 1998).

In addition to glutamatergic and GABAergic input to the cortico-striato-pallido-subthalamic circuit, DA is also involved in modulating the activity of this pathway. Dopaminergic fibres innervate the NAc, ventral pallidum and STh, and DA receptors, either D1-like, D2-like, or a combination have been located in all of the regions comprising this circuit (Magill et al., 2001; Smith and Kieval, 2000). In relation to the NAc, pre-synaptic D1-like receptors attenuate afferent glutamatergic fibres from the PFC (Voorn et al., 2004), and D1-like and D2-like receptors on GABAergic efferents to the ventral pallidum modulate inhibitory control (Smith and Kieval, 2000). Further, the dopaminergic tone of the STh is critically involved in regulating activity of the nucleus and its influence on output regions of the basal ganglia, whereby D2 receptors modulate the local release of both glutamate and GABA (Shen et al., 2003). Overall, the regulation of the cortico-striato-pallido-subthalamic circuit is quite complex and involves an intricate interplay between numerous neurotransmitters.

Importantly, the mesocorticolimbic reward pathway connects with the cortico-striato-pallido-subthalamic circuit at the NAc core and STh. The mesocorticolimbic reward pathway extends from the ventral tegmental area (VTA) to the NAc, ventral pallidum, amygdala, hippocampus and PFC (Koob, 1992). The NAc is a key region of the reward circuit, integral for experiencing reward-related effects after exposure to drugs of abuse (Volkow et al., 2010). In addition to a connection to the reward circuit through the NAc core, the STh also receives direct excitatory projections from the medial PFC (Chudasama et al., 2003; Maurice et al., 1998). The mesocorticolimbic pathway is the main site of action following acute administration of psychostimulants (Luscher and Malenka, 2011). With chronic or repeated use of psychostimulants, the dorsal striatum and wider nigrostriatal pathway are recruited, which are integral for habit formation of compulsive drug taking (Mameli and Luscher, 2011). This pathway communicates with the NAc through the dorsal striatum and the STh through the substantia nigra pars compacta (SNc) and the external segment of the
In addition to recruiting the nigrostriatal pathway, the glutamatergic neurons of the PFC are also implicated in chronic psychostimulant use, as impairments in glutamate regulation are associated with increased motivation to seek and administer psychostimulants, and reduced inhibitory control (Kalivas and Volkow, 2005; Volkow et al., 2011). As the STh receives input from the PFC as well as the mesocorticolimbic and nigrostriatal circuits, it appears that the STh is in a central position to integrate information from regions implicated in chronic drug use to influence cognitive and behavioural outcomes.

In situations involving re-exposure to METH following a period of withdrawal, the VTA is activated, which subsequently increases DA release in the NAc (Robinson and Berridge, 1993). This appears to activate the projections to the PFC, contributing to glutamate release in this region. This would increase the excitation of the glutamatergic projections to the NAc and STh. The activation of the NAc also seems to inhibit the cortico-striato-pallido-subthalamic circuit through activating D2 receptors, inhibiting the STh. Finally, the STh would receive inhibitory input from the nigrostriatal pathway. Considering that the STh would also be receiving increased dopaminergic input from the VTA and SNc (Shen and Johnson, 2000) and more GABAergic input than glutamatergic input, the tonic dopaminergic level would likely be altered, potentially reducing activity in the STh. As the STh would be receiving more inhibitory than excitatory input, the STh would have less control over inhibiting the motivation to, and engagement in, seeking and administering METH.

Considering the known connections between neural circuits involved in drug addiction, together with our findings demonstrating that exogenous oxytocin attenuated relapse to METH-seeking

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**Fig. 2.** The effect of microinjecting oxytocin into the (A) NAc core and (B) STh prior to a METH-priming injection on behavioural output. Amyg, amygdala; GPe, external segment of globus pallidus; GPI, internal segment of globus pallidus; Hip, hippocampus; MDT, medial dorsal thalamus; NAc, nucleus accumbens; PFC, prefrontal cortex; SNc, substantia nigra pars compacta; SNr, substantia nigra pars reticulata; STh, subthalamic nucleus; VP, ventral pallidum; VTA, ventral tegmental area.
behaviour in the NAc core and STh (Baracz et al., 2015, 2016a), this suggests that local administration of oxytocin in these brain regions may have rescued the functioning of these circuits. Indeed, oxytocin microinjected into the NAc core may help to restore the normal functioning of the cortico-striato-pallido-subthalamic circuit so that the STh is disinhibited and able to suppress engagement in compulsive behaviours associated with METH-seeking. Additionally, as suggested above, oxytocin administered into the STh may help recover the normal activity of the region, so that the STh stimulates the output regions of the basal ganglia to inhibit engagement in compulsive drug-seeking behaviours (see Fig. 2). In both regions, oxytocin may be having this effect through activating the OTR as well as the V1a receptor, and interacting with GABA, DA, and glutamate. However, an important consideration is the possibility that other regions are also affected by systemic oxytocin administration in chronic METH models, as the study by Carson et al. (2010b) used an acute METH administration procedure to elucidate the involvement of the NAc core and STh in acute METH processes. Further measures of the effect of oxytocin on cellular activation following repeated METH administration would aim to elucidate additional areas of interest.

It has been suggested that the integrity of the endogenous oxytocin system is important for resilience against addiction and possibly maintaining the regular functioning of the mesocorticolimbic, cortico-striato-pallido-subthalamic and nigrostriatal circuits. In our study examining dysregulation of the oxytocin system following chronic METH self-administration, we showed that oxytocin plasma levels increased following 20 days of self-administering METH, which persisted following 15 days of extinction from drug-taking (Baracz et al., 2016b). Whilst repeated METH administration increased peripheral oxytocin levels, which may contribute to the addiction process, it is also plausible that oxytocin plasma levels could be increased due to the physiological effects of METH use. It is also likely that the increase of oxytocin in plasma at 24 h after the final IVSA session is synchronous with central extracellular oxytocin levels (Carson et al., 2014; Wang et al., 2013; Wotjak et al., 1998) and may be a means to restore the depleted oxytocin system following chronic drug exposure. Polymorphisms to the OTR (Tost et al., 2010) and environmental factors, including exposure to trauma or stressors (Opacika-Juffy and Mohiyeddini, 2012; Unternaehrer et al., 2012), dysfunctional parental attachment (Wismer Fries et al., 2005) and limited or poor social interactions (Branchi et al., 2013) alters the functioning of the oxytocin system and has been associated with increased susceptibility for becoming addicted to drugs of abuse (for a review see Buisman-Pijlman et al., 2014).

Dysregulation to the oxytocin system also likely impacts its regulation of stress, where stressors are known precipitators of relapse to drug use (Koob, 2008). A recent study examining the role of exogenous oxytocin on stress responsivity after social defeat stress showed that intranasal oxytocin administration in stressed male mice increased social behaviours and reduced freezing behaviours, whilst interestingly in stressed female mice, oxytocin reduced freezing behaviours as well as social interaction (Steinman et al., 2016). In female prairie voles, oxytocin-mediated social affiliation has been demonstrated to play a pivotal role in reducing stress. Female voles exposed to 1 h of immobilisation showed a reduction in anxiety-like behaviour, blunted corticosterone response and increased oxytocin release in the PVN when recovering with a male partner compared to alone. Furthermore, this recovery was replicated by the administration of intranasal oxytocin injections following immobilisation in female voles recovering alone (Smith and Wang, 2014). Considering this, it is possible that intranasal oxytocin administration could replenish dysregulated oxytocin levels in drug-addicted individuals, which could be enhanced through concomitant social based therapies.

Preclinical research demonstrates that oxytocin pretreatment in adolescent rodents appeared to be protective against the development of addictive behaviours in adulthood (Bowen et al., 2011; Hicks et al., 2016) and concurrent oxytocin treatment during METH IVSA in adult rats reduced motivation to self-administer METH (Carson et al., 2010a). Whether pre or concurrent oxytocin treatment combined with increased social contact has a synergistic effect on reducing the development of METH dependence has not yet been explored, although it is an important avenue for future research. Altogether, this highlights the importance of a well-regulated oxytocin system as well as the applicability of oxytocin as a restorative treatment for individuals with depleted or dysregulated oxytocin systems.

7. Oxytocin as a pharmacotherapy

The ability of oxytocin administration to attenuate drug reward, craving, and symptoms of withdrawal highlight its applicability as a pharmacological treatment for drug dependency. This potential is strengthened by studies demonstrating that oxytocin itself does not elicit rewarding effects when centrally administered in rodents (Baracz et al., 2012; Qi et al., 2009) and does not reduce motivational behaviours (Gordon et al., 2011; Velazquez-Sanchez et al., 2011). In a human population, nasal delivery of oxytocin appears to be the most effective (Neumann et al., 2013) and non-invasive means of administration as systemically administered oxytocin has poor penetration of the blood brain barrier (MacDonald and MacDonald, 2010) and administration directly to the brain through icv infusion, intracerebral injection, or temporary disruption of the blood brain barrier are highly invasive techniques which are not yet viable options (Lalatsa et al., 2014).

Nasal delivery has been used in psychiatric populations to evaluate the effectiveness of oxytocin in treating the presenting symptoms and associated social and emotional dysfunction. Specifically, the effect of oxytocin intranasal administration in patients with autism spectrum disorder (Anagnostou et al., 2012; Guastella et al., 2010; Hollander et al., 2007, 2003), schizophrenia (Bujanow, 1972, 1974), obsessive-compulsive disorder (Epperson et al., 1996), post-traumatic stress disorder (Pitman et al., 1993), social and general anxiety (Guastella et al., 2009; Labuschagne et al., 2010), and alcohol, marijuana and cocaine dependence (M Crae-Clark et al., 2013; Pedersen et al., 2012; Lee et al., 2014) have been reported with positive findings and no adverse side effects. Considering that oxytocin has mostly been used to improve social deficits and regulate emotion in a variety of disorders, it is likely that oxytocin administration could also improve psychosocial deficits typically apparent in METH abuse and addiction, particularly if used as an adjunct to psychosocial interventions that involve group therapy or stress management.

Intranasal administration is a promising method of administration, however there are a number of factors that need to be further evaluated. To date, it is currently unclear which pathways are used to deliver oxytocin to the brain, although it is thought that the olfactory bulb and trigeminal nerve pathways are the most likely to be activated (MacDonald and Feifel, 2013). However, the efficiency of intranasal oxytocin delivery into the brain has come into question and is coupled with concerns regarding high peripheral oxytocin levels following intranasal administration and the potential unwanted effects this could have on peripheral targets (Leng and Ludwig, 2016). Overall, a greater understanding of the activation of pathways that result in oxytocin reaching the brain in physiologically significant levels following intranasal administration and the potential unwanted effects this could have on peripheral targets (Leng and Ludwig, 2016). Overall, a greater understanding of the activation of pathways that result in oxytocin reaching the brain in physiologically significant levels following intranasal administration in a human population is required, as well as the brain regions that are activated. This will assist in developing more appropriate methods of administration that target the nasal pathways.
responsible for central delivery, as well as the most appropriate dose to be administered, and the most efficient number of sprays per nostril for each administration.

Alternatively, the application of small molecule agonists or positive allosteric modulators that cross the blood brain barrier to activate endogenous oxytocin cells may be a more plausible means of activating the oxytocin system (Young and Barrett, 2015). Indeed, acute melanocortin–4 receptor (MC4R) agonist administration has been shown to release oxytocin in the ventral striatum to help facilitate social attachment in voles (Modi et al., 2015), and to rescue social deficits in mice with a genetic mutation associated with autism spectrum disorder (Ctnnap2; Penagarikano et al., 2015). Further investigation into the use of small molecules such as MC4R to increase oxytocin release and its effect on a range of social deficits and drug dependence will be beneficial for elucidating its feasibility as a more efficient treatment option.

An additional concern of oxytocin treatment is the impact repeated administration has on the brain at a molecular level, as well as on physiology and behaviour. It is likely that in the treatment of drug dependence, repeated oxytocin administration will be required, rather than a one-off dose. To date, most studies involving a human population have only investigated outcomes following acute oxytocin administration (see Table 2 for an overview of factors to consider when evaluating intranasal oxytocin administration studies). A small subset of clinical trials has examined repeated intranasal oxytocin administration over a short period of two to eight weeks with largely positive findings. Daily oxytocin treatment for two to three weeks reduced clinical symptoms (Feifel et al., 2010; Pedersen et al., 2011) as well as improved social cognition (Pedersen et al., 2011) in individuals with schizophrenia, and men with social anxiety experienced an improvement in self-appraisal during public performance tasks when oxytocin was administered weekly in adjunct to four weeks of exposure therapy (Guastella et al., 2009). Outcomes of clinical trials with individuals with autism spectrum disorder are mixed, whereby one study incorporating daily oxytocin administration for six weeks improved clinical symptoms in male adults (Watanabe et al., 2015), whilst eight weeks of twice-daily intranasal oxytocin administration had no effect on symptom presentation in adolescent boys (Guastella et al., 2015). Additionally, as aforementioned, twice daily oxytocin administration for 2 weeks also modulated cocaine craving and drug-related thought processes in cocaine users (Stauffer et al., 2016). To date, one published study has examined the effect of twice-daily oxytocin administration over a long time frame of 7 months on boys aged 10–14 with autism spectrum disorder (Tachibana et al., 2013). Encouragingly, improvements in social interaction and communication were documented. Replication of this study is sorely needed, as well as an expansion into investigating the impact of long-term oxytocin treatment schedules on other psychiatric populations including drug-dependent individuals.

In addition to enhancing understanding of the long-term effects of administering oxytocin in clinical populations, the impact of context and personality factors on the outcome of oxytocin administration should be examined further. The effect of oxytocin administration appears to be context-dependent, where intranasal oxytocin administration has been shown to increase envy and gloating when engaging in a game of chance incorporating monetary gain conditions (Shamay-Tsoory et al., 2009) and increases in-group favouritism and at times out-group derogation in computer-based tasks (De Dreu et al., 2011). Recent studies have also identified that intranasal oxytocin administration can enhance or amplify psychological states; such that oxytocin administration can further decrease trust in individuals with borderline personality disorder who are prone to mistrust (Bartz et al., 2011), and can increase intimate partner violence in men and women who are high in trait aggression (DeWall et al., 2014). This is a particularly salient concern when considering METH dependent individuals and their comorbid psychiatric and behavioural problems, such that their anxiety, depression, psychosis, or aggressive and violent behaviour could possibly be amplified by oxytocin administration and may be influenced by the stage of their addiction. This challenges the view of oxytocin as a purely prosocial peptide and promotes greater consideration of state and trait personality factors and the context within which oxytocin would be administered.

Finally, greater knowledge is required to understand the mechanisms of oxytocin action within the male and female brain for attenuating drug reward and dependence. Considering that oxytocin interacts with the AVP V1a receptor, as well as with DA, glutamate, and GABA, and that the majority of research conducted thus far has focused on the male sex, a greater understanding of the interaction of oxytocin with these systems in both sexes could provide targeted directions for the discovery of effective treatments for drug abuse and dependence.

### 8. Concluding remarks

In recent years, the ability for oxytocin administration to attenuate behaviours associated with illicit and licit drug reward and abuse has been investigated with increased ferocity. Coupled with the involvement of oxytocin in modulating social behaviours, interest in using oxytocin as a potential pharmacotherapeutic
treatment arose as a means of improving social interactions as well as reducing drug craving and relapse. However, the limited understanding of the mechanisms of oxytocin action did limit its application. This review provides an overview of the crucial involvement of the NAc core and STh in oxytocin modulation of METH reward and abuse, and proposes a circuit within which oxytocin could be interacting with neurotransmitters and AVP to attenuate METH related behaviour. Whilst this literature improves our understanding of how oxytocin works to reduce METH reward and abuse in the brain, there are still many unanswered questions. Namely, it is currently unclear whether oxytocin works within additional brain regions to the STh and NAc core to attenuate behaviours associated with chronic METH abuse, and whether oxytocin interacts with other systems, such as the V1a receptor, DA, GABA and glutamate neurotransmitters to produce these effects. There is much more to uncover about the action of oxytocin treatment, however we know that it plays an important role in mediating METH-related reward and abuse. Future investigation will unravel the mechanisms of oxytocin action to gain evidence for efficacious pharmacotherapies for drug addiction.

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