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Review

# Individual differences underlying susceptibility to addiction: Role for the endogenous oxytocin system☆

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ABSTRACT

Recent research shows that the effects of oxytocin are more diverse than initially thought and that in some cases oxytocin can directly influence the response to drugs and alcohol. Large individual differences in basal oxytocin levels and reactivity of the oxytocin system exist. This paper will review the literature to explore how individual differences in the oxytocin system arise and examine the hypothesis that this may mediate some of the individual differences in susceptibility to addiction and relapse.

Differences in the oxytocin system can be based on individual factors, e.g. genetic variation especially in the oxytocin receptor, age or gender, or be the result of early environmental influences such as social experiences, stress or trauma. The paper addresses the factors that cause individual differences in the oxytocin system and the environmental factors that have been identified to induce long-term changes in the developing oxytocin system during different life phases.

Individual differences in the oxytocin system can influence effects of drugs and alcohol directly or indirectly. The oxytocin system has bidirectional interactions with the stress-axis, autonomic nervous system, neurotransmitter systems (e.g. dopamine, serotonin and GABA/glutamate) and the immune system. These systems are all important, even vital, in different phases of addiction.

It is suggested that early life adversity can change the development of the oxytocin system and the way it modulates other systems. This in turn could minimise the negative feedback loops that would normally exist. Individuals may show only minor differences in behaviour and function unless subsequent stressors or drug use challenges the system. It is postulated that at that time individual differences in oxytocin levels, reactivity of the system or interactions with other systems can influence general resilience, drug effects and the susceptibility to develop problematic drug and alcohol use.

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*Abbreviations:* AVPRV1, arginine vasopressin receptor 1; BNST, bed nucleus of the stria terminalis; CNS, central nervous system; CPP, conditioned place preference; CRF, corticotropin releasing factor; CSF, cerebrospinal fluid; HPA, hypothalamic–pituitary–adrenal; ICV, intracerebroventricular; i.p, intraperitoneal (injection); LG, licking grooming (maternal rat behaviour); MDMA, 3,4-methylenedioxy-N-methylamphetamine or ecstasy; NAcc, nucleus accumbens; OXT, oxytocin; OXTR, oxytocin receptor; PFC, prefrontal cortex; PVN, paraventricular nuclei of the hypothalamus; SON, supraoptic nuclei of the hypothalamus; VTA, ventral tegmental area.

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## 1. Introduction

Addiction is a major problem worldwide that directly and indirectly affects a large percentage of the population. According to the United States Substance Abuse and Mental Health Services Administration's (SAMHSA's) National Survey on Drug Use and Health, 8.7% of US population aged 12 or older received treatment for an illicit drug or alcohol abuse problem in 2010 (22.1 million; SAMHSA, 2011). The majority of these people sought help for alcohol dependence, with 15 million people in treatment for alcohol dependence alone, while another 2.9 million were treated for dependence on both alcohol and illicit drugs.

However, these statistics only represent a small portion of the people that struggle with alcohol and drug use. There are large differences among individuals in the capacity to manage alcohol and drug use, which seem to be based on genetic variation, the environment and personal factors (Wichers et al., 2013). Some people respond strongly to the rewarding effects of drugs, while others experience many side effects. Drugs can also fulfil different roles in someone's life; some people may rely on alcohol to calm their anxiety, while others may only develop a problem with its use in the context of a traumatic event (e.g. the death of a loved one). Studies going back to the 1980's have shown that oxytocin is able to affect drug effects and addiction processes (Ibragimov et al., 1987; Kovács et al., 1985, 1998). Most current studies focus on the effects of exogenous oxytocin on drug effects and relapse, however, individual differences in the endogenous oxytocin might explain some of the individual differences seen in susceptibility to addiction. This paper will postulate that early adversity can influence the developing oxytocin system and affect susceptibility to addiction (Fig. 1). Special attention will be paid to potentially critical periods when specific environmental influences may induce lifelong changes.

This paper will focus on the direct effects of the neuropeptide oxytocin and the modulatory effects of oxytocin on several key systems that have been implicated in the biology of addiction. The overlap between the neurocircuitry for affiliative and drug-taking behaviour was described by Insel (2003), focusing on the oxytocin, vasopressin and mesolimbic dopamine system. The focus of the present review will be even broader, also considering the interactive roles in addiction of neurotransmitter systems, of the hypothalamic–pituitary–adrenal (HPA) axis, the immune system and the effects on the central nervous system (CNS) and behaviour. We will postulate that a well-regulated oxytocin system can increase resilience and reduce the probability that an individual will develop an addiction by both direct effects, and interactions with other key systems.

The paper will provide an overview of several key biological systems implicated in the biology of addiction, focussing on neurotransmitter systems, HPA-system and immune system. It will then focus on providing an overview of the endogenous oxytocin system and importantly on individual differences in the oxytocin system. Subsequently, the documented effects of exposure to environmental factors on the endogenous oxytocin system are analysed for different life phases (prenatal, early life, childhood, adolescence and adulthood) and possible outcomes are discussed. The focus then shifts to the direct effects of oxytocin on drug effects and addiction, and its ability to modulate key biological systems implicated in the biology of addiction; special attention will be paid to bidirectional interactions with the mesolimbic dopamine system, HPA-axis, serotonin system, glia and peripheral immune system, and Vagus Nerve. To conclude, a model for the possible involvement of the endogenous oxytocin system in addiction is described and the strengths and weaknesses of the theory are discussed.

## 2. Addiction and individual differences

Addiction extends beyond using drugs often and in large quantities. It is characterised by the development of tolerance and physical or psychological dependence, as well as by increased time spent using or

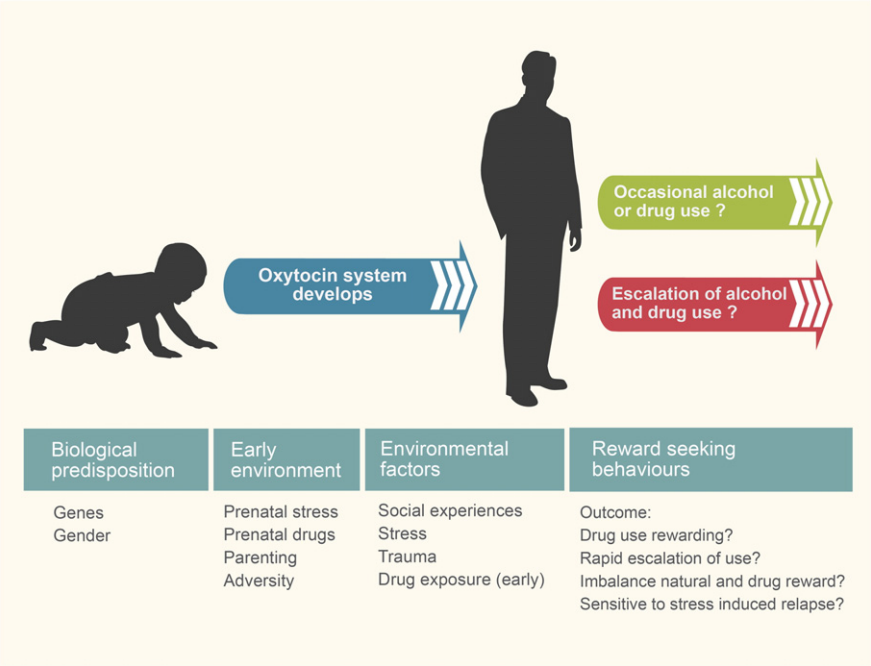


**Fig. 1.** Suggested model: individual factors and (early) environment shape the development of the oxytocin system affecting susceptibility to addiction. Substantial individual differences exist in basal oxytocin levels and reactivity of the system. The endogenous oxytocin system changes and matures over time as part of normal development. This paper postulates that individual factors and environmental factors influence the developing oxytocin system affecting oxytocin levels and responsiveness of the oxytocin system. Different factors are important in different life phases, depicted as a biological predisposition, influences of early environmental factors and later environmental factors. When an individual is exposed to alcohol and drugs in adolescence, these individual differences in the endogenous oxytocin system can affect reward seeking and drug use behaviour. It is postulated that for example drug use may be more rewarding resulting in an escalation of use; an imbalance between natural and drug rewards could affect the attractiveness of excessive drug use; individuals may be more susceptible to stress-induced relapse to drug use.

obtaining drugs (American Psychiatric Association, 2000). Addiction also is defined by the inability to control the drug use or stop using, and may include the experience of withdrawal on cessation of use. Drug or alcohol abuse interferes with an individual's normal activities, but may be continued despite its negative consequences. In addiction research, different phases are described such as initiation, escalation, dependence, withdrawal and relapse. Behavioural, psychological and physiological measures are used to study these phases. Most experimental research studying the development of dependence occurs in animals, while research into the individual differences in susceptibility to addiction in humans is based on epidemiological studies, brain imaging and genetic studies. This paper will draw on both animal and human multidisciplinary data to elucidate the role of endogenous oxytocin in addiction.

Animal research has focussed on individual differences within and between strains of animals in drug seeking and development of addiction. For example, behaviourally impulsive animals show increased responses to drugs of abuse (Dalley et al., 2011; Marusich et al., 2011; Yates et al., 2012). Environmental influences can also induce individual differences in gene by environment interactions. For example Ellenbroek et al. (2005) developed an animal model based on two extremes within a normal rat population. They selected animals, with distinctly different responses to a dopamine agonist (APO-SUS and APO-UNSUS). These animals also responded differently in alcohol and cocaine self-administration tests, while environmental stressors could modify behaviours. Genetic differences were recorded, however the authors concluded that a gene by environment effect was likely to be the major contributor to differences in drug-taking behaviour.

Moffett et al. (2007) reviewed animal studies studying the long-term differential effects of distinct maternal separation protocols; these showed long-term effects of separation on subsequent alcohol intake patterns. In mice, prenatal stress has also been associated with a greater motivation for, and consumption of, alcohol in adulthood.

Human studies have also focussed on gene and environment interactions affecting drug abuse and addiction. As one example, longitudinal data from epidemiological studies indicate that experiencing maltreatment and cumulative stressful life events prior to puberty, and particularly in the first few years of life, were associated with an early onset of problem drinking in adolescence and with an increased likelihood of alcohol and drug dependence in early adulthood (Enoch et al., 2010).

Recent developments in genetic research and imaging have advanced the capacity to study the biology of human addiction. Twin studies have shown that both shared environment (for example, socio-economic factors) and genetic factors have a strong influence on the initiation of drug use (Agrawal and Lynskey, 2008; Munafò and Johnstone, 2008; Verweij et al., 2010). Genes implicated in stress, anxiety, attention, learning and memory and reward processing have been the recent focus in addiction research. Increased impulsivity and attention deficit hyperactivity disorder (Chang et al., 2012) is also associated with an increased likelihood of addiction, possibly because of a tendency toward early experimentation with drugs or alcohol. Major life events or traumas may also increase the vulnerability to develop drug dependence. Among the factors that have been implicated in addiction are sensitivity to reward (for example, polymorphisms in the dopamine receptor), differences in enzyme activity (for example, alcohol metabolism) and social factors (such as peer and parental attitudes). Neurobiological differences underlying severity of craving and responsiveness to cue- or stress-induced relapse strongly affect how easily people quit smoking. Addiction is a complex disease regulated by a number of genes. The main emphasis in recent years has been on the role of gene by environment interactions (Enoch, 2011; Enoch et al., 2010) and on the effects of polymorphisms in genetic pathways (Reimers et al., 2012) that are involved in the neurobiology of addiction. One step further would be to examine epigenetic changes; for example, due to oxygen deprivation during birth or continued use of drugs of abuse which may have epigenetic consequences, which in turn would alter

gene expression (Caldji et al., 2011; Maze and Nestler, 2011; Renthal and Nestler, 2008), with potential consequences, for example, for sustained drug dependence.

Advances in a diverse range of imaging techniques have increased our understanding of brain areas involved in drug effects and in responses to associated cues. These methods have permitted visualisation of differences in responses to the environment and decision making tasks that are important in understanding the underlying biology of addiction (reviewed Parvaz et al., 2011; Volkow et al., 2012). Another recent area of research combines neural imaging with an analysis of genetic and environmental factors. Thus it becomes possible to examine individual variability in reinforcement behaviour in the context of individual differences in neural activation (Loth et al., 2011).

## 3. Biology of addiction: identifying the major players

Addiction is a complex disorder; the biological basis of addiction mirrors this complexity. Studying addiction goes beyond examining direct effects of a drug and includes: a focus on memory of the experience and setting associated with drug use; decision making such as choosing between short and long-term gain; loss of control; identifying triggers for use, and so forth. It is likely that we do not yet have a full overview of the systems that are involved or how they influence each other. Although drugs exert their effects via different receptor systems, several brain regions are involved in drug abuse in general. Brain regions that are central to drug reward are part of the mesolimbic dopamine pathway, including the nucleus accumbens (NAcc) and the ventral tegmental area (VTA). These regions extend to the prefrontal cortex (PFC), which is critical for executive functioning and decisions concerning drug use. The dopamine reward pathway seems to be central in robust drug reward. However, recent publications providing a broader perspective on drug reward, suggest non-dopaminergic mechanisms of reward as well (Ikemoto, 2010; Volkow et al., 2011). The limbic system (including the VTA, NAcc and hippocampus) as a whole is important in emotion, drive, and memory processes that affect addiction. The HPA-axis is also a player that influences continued drug use, withdrawal and relapse (Koob, 2008).

The role of major brain regions in specific brain processes related to addiction is reviewed elsewhere (Parvaz et al., 2011). The systems listed below are of particular importance as they play an important role in addiction and they are influenced by the oxytocin system. However, this list is not comprehensive, covering only a subset of factors that have been implicated in addiction.

### 3.1. Neurotransmitters

Existing research has mainly focussed on the role of neurotransmitter systems in drug effects and the development of addiction. Different drugs act on different neurotransmitter systems, but nearly all drugs of abuse eventually result in an increase in dopamine in the mesolimbic dopamine system reward pathway (Pierce and Kumaresan, 2006). Neurotransmitter systems that are key to drug effects are the dopamine system (for example, stimulants and MDMA), opioid system (heroin, codeine and alcohol), serotonin (for example, MDMA and hallucinogens), GABA and glutamate (for example, alcohol and benzodiazepines), and the cannabinoid system (cannabis) (Parolaro et al., 2005). Beyond their role in direct drug effects, many of these systems seem to be involved in susceptibility to the development of addictions (Buisman-Pijlman et al., 2009; Maldonado et al., 2006; Mechoulam and Parker, 2013; Parolaro et al., 2005).

### 3.2. Stress and the hypothalamic–pituitary–adrenal (HPA) axis

Stress can increase vulnerability to drug addiction (see introduction) and trigger relapse to alcohol and drug use after a period of abstinence (Shalev et al., 2010). Sinha et al. (2011) provide a good overview of the role stress can play in relapse and how stress can trigger strong craving. Because users often continue drug use to avoid withdrawal the negative reinforcement of drugs can become more important than the positive reinforcement effects. Several studies looking at continued drug use and withdrawal have focussed on the role of corticotropin releasing factor (CRF; Koob, 2008); CRF is an central factor in the regulation of the HPA-axis in response to stress, and CRF has been implicated in the negative reinforcing effects of drugs after prolonged drug use (Koob, 2008).

### 3.3. Immune system

In recent years, a new player has been implicated in the neurobiology of addiction: the immune system. The immune system can alter neuronal signalling in the brain with consequences for behaviour and cognition. A large part of the brain consists of supportive, non-neuronal tissue such as glia. This "supportive" tissue also regulates brain function. Oliet et al. (2008) demonstrated that glia processes were able to affect neuronal signalling of glutamate and GABA signalling. Additionally, cytokines are immune modulators, involved in creating a pro-inflammatory state that can influence how the body responds to subsequent challenges (illness or stressors). A "primed" immune system, in which the body is in a pro-inflammatory phase, seems to increase the risk for several psychopathologies such as addiction, depression and pain (Dantzer et al., 2008). For example, animal studies have shown that postnatal stress can cause a pro-inflammatory phase, which later affects drug withdrawal in mice (Schwarz et al., 2011). Changes in the immune system are capable of increasing direct drug rewards (Hutchinson et al., 2012). Although we do not fully understand the mechanism through which the immune system affects addiction behaviour, it interacts with several key systems (like dopamine and HPA-axis) that are central to addiction.

### 3.4. Oxytocin

Neuropeptides have been of interest to addiction research for several decades but have not taken centre stage. In the 1980s, the effect of oxytocin administration became a focus of preclinical addiction research (Kovács et al., 1998; Sarnyai and Kovacs, this issue). Vasopressin is a related nonapeptide which is produced and released from some of the same brain regions as oxytocin, but with different functions in the body (Neumann and Landgraf, 2012). As oxytocin and vasopressin have affinity for each other's receptors, findings on vasopressin are also mentioned here at crucial points.

Several clinical studies have investigated the effect of intranasal oxytocin in relapse to addiction (clinicaltrials.gov), although available data in humans are generally preliminary, there are indications that exogenous oxytocin may have benefits in addiction (Pedersen et al., 2012). However, the current paper will focus on the evidence for a role in addiction of the endogenous oxytocin system. Before the role of oxytocin in addiction is described, we will provide an overview of the endogenous oxytocin system and factors affecting individual differences in oxytocin level and receptors.

## 4. Endogenous oxytocin system

### 4.1. Oxytocin synthesis

Oxytocin is a neuropeptide consisting of 9 amino acids. It was functionally identified in 1906 by Sir Henry Dale, and described chemically in the 1950s by Vincent Du Vigneaud (Lee et al., 2009). Oxytocin synthesis in the central nervous system (CNS) primarily takes place in the paraventricular nucleus (PVN) and the supraoptic nucleus (SON) of the hypothalamus. The majority of oxytocin is transported to the posterior pituitary where it is released into the bloodstream, with effects on tissues throughout the body (Leng et al., 2011; Quirin et al., 2011).

Oxytocin is also synthesized in various peripheral tissues and organs, including the uterine epithelium, ovary, testis, vascular endothelium cells and heart (Nishimori et al., 2008).

### 4.2. Regulation of release

Release of oxytocin by the posterior pituitary into the blood stream is triggered by vaginocervical and nipple stimulation (Nishimori et al., 2008). However, oxytocin also may be released by positive social stimuli including close physical contact in a safe environment; exposure to infants and orgasm; in addition, noxious stimuli; conditioned fear; novel environments (Burri et al., 2008; Carter, 19921998; Feldman et al., 2012; Kenkel et al., 2012; Neumann and Landgraf, 2012; Opacka-Juffry and Mohiyeddini, 2012; Pournajafi-Nazarloo et al., 2013; Sasayama et al., 2012; Uvnäs-Moberg, 1998).

A variety of studies in healthy humans have reported large and reliable individual variations in plasma levels of oxytocin. For example, Opacka-Juffry and Mohiyeddini (2012) using enzyme-immunoassay in unextracted samples report plasma (venous blood) oxytocin concentrations in men, ranging from 79 to 1198 pg/ml, with an average of 378 pg/ml. Similar ranges are seen in studies by Feldman et al. (2012); Weisman et al. (2013) and in Gouin et al. (2010), with even more individual variation seen in clinical populations such as Williams Syndrome (Dai et al., 2012). Comparisons across studies can be difficult since values may differ depending on the analysis techniques that was used (Szeto et al., 2011). However, recent evidence from mass spectrometry revealed that oxytocin (as well as vasopressin) levels can reach the ng/ml range in plasma. These peptides are sequestered by binding to plasma proteins, possibly delivering these hormones to tissues as needed, with beneficial consequences especially in the face of challenge (Martin and Carter, 2013).

Relative amounts of gene expression for oxytocin and vasopressin also support the hypothesis that these peptides are available in great abundance (Gautvik et al., 1996). In the CNS these peptides can be released from both synapses and axons in the brain and can diffuse into other brain areas (Borrow and Cameron, 2012; Campbell et al., 2009; Ishak et al., 2011). Cells originating in the PVN have specific pathways which efficiently deliver oxytocin to other structures in the brain including the amygdala, bed nucleus of the stria terminalis (BNST), lateral septum, hippocampus and NAcc (Stoop, 2012).

Several studies demonstrate that oxytocin is more readily released in situations where a social component is present (Feldman et al., 2012). For example, oxytocin levels in calves are increased by suckling from their mother, but not when drinking the same milk from a bucket (Lupoli et al., 2001). Additionally, oxytocin can also reduce pain or HPA-axis reactivity after stress (Dabrowska et al., 2011), but only when a social partner is present. This highlights the importance of social interaction in the release and actions of oxytocin.

### 4.3. Central and peripheral levels

Oxytocin can be released in the periphery and centrally, as described above. Oxytocin released by peripheral organs or by the posterior pituitary does not readily cross the blood–brain barrier (BBB), with only 1–2% crossing (Opacka-Juffry and Mohiyeddini, 2012). Veening and Olivier (2013) discuss possible other ways in which oxytocin can pass from the periphery to the brain and back. McEwen (2004) reports that oxytocin seems to be transported by a saturable carrier; disappearance rate from the brain for $^{125}$I-oxytocin was 19.1 min. Oxytocin may be able to cross the foetal, or a damaged BBB, more readily. For example, addiction may induce leakage of peptide from the blood to the cerebrospinal fluid (CSF; Kovács et al., 1998; Nishimori et al., 2008). BBB permeability can also be affected by, for example, hypertension, stress or disease (Churchland and Winkielman, 2012).

It is unclear what percentage of peripherally administered oxytocin reaches oxytocin receptors in the brain. However, research dating back to the 1980s shows that a significant amount of peripherally injected oxytocin does reach the brain (Carson et al., 2010a, 2010b; Kovács and Telegdy, 1988; Neumann et al., 2013; Van Ree and De Wied, 1977). A recent review by Veening and Olivier (2013) sheds light on our current (limited) understanding of how intranasal oxytocin reaches the brain. However, oxytocin levels measured in the blood may not directly represent concentrations in specific brain regions (Opacka-Juffry and Mohiyeddini, 2012). However, as oxytocin is released by the hypothalamus into the blood, measurements of peripheral oxytocin may serve as a relative approximation of hypothalamic hormone production.

### 4.4. Receptor

Until now, only one oxytocin receptor has been identified: the oxytocin receptor (OXTR). It is widespread in the brain and body in a sex-and species-specific manner (Georgescu et al., 2003; Lee et al., 2009). OXTR is expressed in the mammary gland, uterine myometrium, adipose precursor cells, gastrointestinal tract, cardiac muscle of the heart, and vascular endothelium layer (Gimpl and Fahrenholz, 2001; Ohlsson et al., 2006; Nishimori et al., 2008). A high density of OXTR can be found in brain regions involved in regulating mood, social behaviour and addictive processes (Burri et al., 2008; Sarnyai, 2011), such as the cortex, hippocampus, VTA, NAcc, hypothalamus, ventral pallidum, limbic system, basal ganglia, medial preoptic area, olfactory bulbs, (central) amygdala and brain stem (Gimpl and Fahrenholz, 2001). The OXTR receptors in the periphery and central nervous system are considered to be the same (Nishimori et al., 2008).

The OXTR is a member of the G-protein coupled receptor family and is 388 amino acids in length (Nishimori et al., 2008). Activation of OXTR by the binding of OXT to its outer membrane domain activates G-protein alpha subunit, phospholipase C and protein kinase C, and finally activates numerous cellular proteins and accelerates the outflow of Ca++ from the endoplasmic reticulum, leading to several downstream cellular responses. Interestingly, differences in downstream processes after activation of the receptor in different sites in the body seem to facilitate diversity in functions of oxytocin. Although oxytocin binds only to one type of receptor, the receptor couples to two different G proteins, Gq/11 at its proximal portion of the C-terminus and to Gi/o (Hoare et al., 1999). Since then papers have explored how these different signalling pathways could facilitate the diversity in functions that oxytocin displays (Chini and Fanelli, 2000; Devost et al., 2008). Gimpl et al., 2008; Rimoldi et al., 2003).

Additionally, dramatic up- and down-regulation takes place in specific periods of life (for example around parturition; Devost et al., 2008). The dynamic changes in expression of the oxytocin receptor, and the different downstream processes in specific regions after activation, offer a source for individual variability.

Oxytocin also has affinity for the vasopressin receptor and vice versa (Ohlsson et al., 2006); three vasopressin receptor subtypes have been identified V1a, V1b and V2. The maximum effect of oxytocin and vasopressin on contractile movement in the uterus is comparable, but oxytocin is more potent in exerting its effect (Nishimori et al., 2008). Several well-known agonists for the oxytocin receptor also have high affinity for the vasopressin receptor 1a (AVPRV1a; Lee et al., 2009).

Lemaire et al. (2002) suggest that the oxytocin and vasopressin AVPRV1a receptors (and not AVPRV1b) are the predominant receptor subtypes in rat brain and spinal cord; distribution is receptor specific. Comprehensive information on specific affinity and efficacy of the different oxytocin and vasopressin receptors can be found in Chini et al. (2008).

### 4.5. Functions of oxytocin

Oxytocin is implicated in the regulation of a wide range of behaviours and physiological responses. Oxytocin is well known for its role

in parturition, lactation and pair bonding (Lee et al., 2009; Waldherr and Neumann, 2007). However, oxytocin is also thought to increase interpersonal trust, reduce anxiety, reduce stress responses, reduce immune and inflammatory response, alter memory and information processing, and reduce pain (Bartz et al., 2011; Baskerville and Douglas, 2010; Carter, 1998; Lemaire et al., 2002; McGregor and Bowen, 2012; Sarnyai and Kovács, 1994; Smith and Wang, 2012; Tops et al., 2012; Uvnäs-Moberg, 1998; Veenema and Neumann 2008; Waldherr and Neumann, 2007; Weisman et al., 2012). However, it is important to note that not all subjects respond positively to oxytocin when given exogenously (Bartz et al., 2011).

The aim of this paper is to investigate the role of oxytocin in drug effects and addiction, which will be discussed extensively in Section 6.

## 5. Individual differences in the endogenous oxytocin system

Oxytocin seems to mediate a large range of effects, but research shows that individual differences in oxytocin levels are quite large. Human research shows large differences not only in basal levels of oxytocin, but also in response to challenges which have been correlated with various behavioural differences (Gouin et al., 2010; Weisman et al., 2012).

Additionally, individual-, species- and sex -specific differences exist in the abundance of central oxytocin receptors (Carter, 2007; Phelps et al., 2010).

The following differences in the oxytocin system could have functional outcomes that translate into behavioural differences: expression of oxytocin and its receptor; number, location and sensitivity of receptors; and connectivity with other systems.

Only limited research has been conducted on the origin of these individual differences. Individual differences can be based on age, gender and genetic differences. Large differences also seem to exist between species in the distributions of oxytocin (and vasopressin) receptors that appear to correlate with the sociality of these animals (Shapiro and Insel, 1989; Witt et al., 1992).

At least some differences are induced by the environment, such as early experiences and other environmental factors for example drug use (Bales et al., 2011). Since the oxytocin system continues to develop during the postnatal and adolescent periods in rodents (Nylander and Roman, 2012) and humans (Bales and Perkeybile, 2012), the following factors might be able to contribute to the observed individual differences: early life adversity; parenting; social experiences; gene x environment interactions; differential susceptibility; epigenetic factors; and drug-induced changes.

The following sections will discuss the individual differences in the endogenous oxytocin that have been observed based on individual and environmental factors. Lastly, the paper will report on the possible effect of the age at which exposure to these environmental factors took place.

### 5.1. Individual factors

#### 5.1.1. Gender differences

In general, sex differences are not seen in peripheral blood levels of oxytocin. However, sex steroids can affect both oxytocin synthesis and receptors (Gimpl and Fahrenholz, 2001). Looking at the role of sex hormones, we know that oxytocin receptor expression is affected by oestrogen (Young et al., 1997). Interestingly, neonatal oxytocin can also alter oestrogen receptor alpha expression and oestrogen sensitivity in female rats (Perry et al., 2009).

Additionally, oxytocin responses to stress may be sexually dimorphic, especially during early life as shown in animal studies (Bales et al., 2011). Carter et al. (Heim et al., 2009) reviewed gender-specific differences in the effects of prenatal and early life stress on the oxytocin and vasopressin receptors. Studies from animals suggest a particularly important role for oxytocin and changes in that pathway in females, while vasopressin pathways, especially in the central nervous system, may be of special relevance to males.

The role of sex steroids in gender differences, and in oxytocin receptor binding and expression, could also be at the basis of disparities reported in human studies (Opacka-Juffry and Mohiyeddini, 2012).

#### 5.1.2. Genetic differences

Individual differences in the oxytocin gene or receptor can cause changes in basal levels, or responses after stimulation of the receptor. Polymorphisms in the oxytocin gene and the oxytocin receptor gene have been linked primarily to differences in stress reactivity and empathy, changed perception of social cues, aggression, attachment, and parenting (Ebstein et al., 2012; Feldman et al., 2012; Malik et al., 2012; Rodrigues et al., 2009). Importantly, Tost et al. (2010) demonstrated using neuroimaging techniques structural and functional alterations in the brains of (human) male and female carriers of the OXTR risk allele (focusing on rs53576). They observed that structural alterations in key oxytocinergic regions emerged, particularly in the hypothalamus. Importantly, these neural characteristics predicted lower levels of reward dependence, specifically in male risk allele carriers. They identified a sex-dependent difference that is of interest for the current paper. Additionally, oxytocin gene polymorphisms have also been demonstrated to influence dopamine function in humans (Love et al., 2012). Recent unpublished research by this group also shows a change in alcohol use in adolescents with a variation in the oxytocin gene (Glaser et al., 2013). A variation in this gene (rs4813625) explains individual variation in adolescent alcohol drinking, and imaging studies suggest that this effect is mediated by an interaction with the dopamine system and is sex dependent.

Interestingly, two OXTR polymorphisms (rs4564970 and rs1488467) were shown to moderate alcohol induced aggressive behaviour in adult men (Johansson et al., 2012a, 2012b).

Williams Syndrome is an illness that has recently been linked to an overproduction of oxytocin and vasopressin in response to specific stimuli such as music (Dai et al., 2012) based on a genetic mutation. People with this syndrome show developmental delays and mental retardation, while being overly friendly and trusting. Some individuals with this condition produce very high levels of oxytocin in response to either music or an aversive stimulus. In Williams Syndrome, oxytocin was negatively correlated with adaptive social behaviours. However, the status of the oxytocin receptor needs to be studied before drawing conclusions about the implications of these findings, since prolonged exposure to high levels of oxytocin might down-regulate the receptor. No papers are available on alcohol and drug use in people with this syndrome, but it would be interesting to know if they have reduced vulnerabilities to addiction.

Oxytocin knockout animals show reduced flexibility in behaviour (Sala et al., 2011). Amico et al. (2005) showed that adult knockout mice showed increased levels of sucrose intake when tested in a two bottle-choice paradigm; this difference was sustained over several testing day. They replicated this finding using the non-caloric saccharin (Billings et al., 2006) and even showed that stress did not diminish this increase. These findings seem to show that the endogenous oxytocin system is involved in limiting intake of new and familiar palatable substances and that stress-induced anhedonia is disturbed in knockout mice.

Interestingly, McGregor and Bowen (2012) postulated that extreme dopamine stimulation without oxytocin stimulation results in object-oriented behaviour such as that seen in autism (with a disproportionally high prevalence in males) and addiction. Hollander et al. (2003) demonstrated that oxytocin levels were reduced in children with autism, and that disturbances in repetitive behaviour could be normalised with (intranasal) oxytocin (Hollander et al., 2003; Modahl et al., 1998). Generalities regarding endogenous oxytocin in autism may be premature, since studies are rare and the origins of these differences remain to be determined. The literature regarding the role of oxytocin in disorders

such as autism is complex, possibly reflecting individual differences, diagnostic variation or age.

*5.1.3. Age and development of the oxytocin system*

The endogenous oxytocin system starts to develop in utero and continues to develop during the postnatal period and adolescence in rodents (Nylander and Roman, 2012) and humans (Bales and Perkeybile, 2012). Detailed information on the development of the oxytocin system is mainly derived from animal studies using rats and prairie voles; for a review see Bales and Perkeybile (2012). OXTR in the rat brain is present during the entire period of development, whilst prairie voles show transient expression and reorganisation (Bales and Perkeybile, 2012). Rat studies show that receptor affinity of the oxytocin receptor does not seem to change during development, with infant receptors being functional already. However, OXTR density changes with age in rats and is also influenced by maternal separation (Lukas et al., 2010). Most notably, OXTR binding density in the caudate putamen showed a 2-fold decrease while OXTR binding in the ventromedial hypothalamus showed a 4-fold increase with age. The functional significance of regional differences in the OXTR remains largely unexplored.

*5.2. Environmental factors and life phase*

The development and functioning of the oxytocin system seems to be sensitive to external influences such as social environment, stress and illness. As the oxytocin continues to develop after birth (5.1.3), timing of these external influences can affect the final outcome. Data also show that the adult oxytocin system retains plasticity, which makes it responsive to external stimuli and naturally-occurring changing demands in life such as around lactation and parturition.

The following section will discuss the influences that can alter the endogenous oxytocin system prenatally, in infancy, adolescence or adulthood.

*5.2.1. Prenatal period: stress and drug exposure*

Factors affecting oxytocin system during this period mainly relate to the affect of prenatal stress and drug exposure.

Exposing pregnant rat dams to unpredictable stressors during the last week of gestation resulted in changed social behaviour (reduced social drive) and reduced levels of oxytocin mRNA in the paraventricular nucleus, and increased oxytocin receptor binding in the central amygdala in male offspring (Lee et al., 2007). De Souza et al. (2013), also showed the long-term effects of prenatal stress exposure (restraint) in the same period on social behaviour, but focussed on the number of oxytocin neurons in the PVN and SON in adult rats. Animals were cross-fostered to prenatally stress or not-prenatally stressed mothers. Only the combination of being exposed to prenatal stress and being raised by a prenatally-stressed rat dam resulted in adult male offspring with a decreased number of OXT-positive magnocellular neurons, VP-positive magnocellular and parvocellular neurons of the PVN. No changes were shown in the OXT and VP cellular composition of the SON nucleus. Animals showed increased anxiety-like behaviour and aggressiveness.

Prenatal alcohol and drug exposure was able to alter OXT levels and receptor binding in specific regions. Johns et al. (1998) clearly demonstrated that gestational cocaine exposure causes long-term decreases in OXT levels in hippocampus, hypothalamus and preoptic area. Williams et al. (2009) also showed that the combination of prenatal alcohol and nicotine exposure affects oxytocin receptor binding, ethanol consumption and preference. Oxytocin receptor binding in the NAcc and hippocampus was increased in prenatally-exposed adult males only. Prenatal exposure to both of these drugs sex-specifically decreased ethanol preference behaviour in offspring, unlike reports for either drug separately; this effect was different in different age groups. For a comprehensive review of the distinction between the impact of gestational cocaine exposure and the effect of cocaine on parental behaviour in rat dams please refer to Williams and Johns (2014).

*5.2.2. Infancy and early life: maternal separation and attachment*

Extensive research focuses on the long-term effects of early life adversity and social environment on the oxytocin system, although most studies use animal research. Maternal and social interactions during the neonatal period organize the subsequent expression of behaviour by altering sensitivity to neuropeptides including oxytocin and vasopressin (Bales et al., 2011; Cushing and Kramer, 2005).

Furthermore, in humans the oxytocin system seems to be sensitive to positive early social experiences and negative experiences such as separation (Feldman et al., 2012). A positive effect of the environment on oxytocin levels has been reported in infants who had experienced high affect parent-infant synchrony (i.e. monitoring and responding). These infants showed increased oxytocin saliva measures compared to infants reared in the presence of low affect synchrony (Feldman et al., 2010b); these children also showed more social competence. Tops et al. (2014-in this issue) explore the effect of attachment and oxytocin on engagement of cortical loops, exploring whether oxytocin is involved in the overlapping mechanisms of stable attachment-formation and stress-coping.

Looking at the impact of social deprivation, Wismer Fries et al. (2005) reported that the oxytocin system was affected in children who had been exposed to extremely adverse early upbringing directly after birth. Children who were raised in institutions in Romania before they were adopted into a family showed altered oxytocin *reactivity* when tested at the age of 4. Basal urine oxytocin levels were the same, but adopted children did not show an increase in oxytocin levels during physical contact with their adopted parent or a stranger. Control children raised in family environment did show an increase, but only when contact was with their own parent. [Note: Although concerns have been raised about the validity of the measures and analysis in this experiment (Anderson, 2006), the differences were based on within-subject measurements supporting the internal validity of this study].

Early life stress (based on questionnaires) was linked to lower oxytocin levels in healthy adult males; the effect was moderated by trait anxiety (Opacka-Juffry and Mohiyeddini, 2012). Early parental separation in humans was also associated with decreased salivary cortisol excretion in response to intranasal oxytocin in young males (Meinlschmidt and Heim, 2007).

Although studies of mechanism are relatively rare in humans, more detailed information is available from animal research. Veenema (2012) provide a good review of the effects of early-life manipulations in rodents on the distribution of oxytocin and vasopressin receptors and on their expression. In general animal models examine the effects of both deprived and enriched early environments, and these show that differences in the quality of the early social environment are associated with brain region-specific alterations in oxytocin and vasopressin expression, and oxytocin receptor and vasopressin 1a receptor binding. However, apparently small differences in early experience, such as a single handling experience in early life possibly mediated by maternal behaviour, can have profound and lasting consequences for later behaviour in the offspring (Bales et al., 2011).

Maternal separation in rodents is a commonly-used model to investigate postnatal stress, although differences in, for example, separation duration can affect outcome. Nylander and Roman (2012) analysed the effect of early life stress on oxytocin and alcohol drinking in animals. Altered levels of oxytocin were observed in specific brain regions (e.g. hypothalamus, pituitary and amygdala), however, this change was not linked to changes in ethanol consumption in male rats (Oreland et al., 2010).

Lukas et al. (2010) specifically investigated the effect of maternal separation on OXTR and AVPRV1a in juvenile, adolescent and adult rats. They found that maternal separation (3 h daily, PND 1–14) caused robust age-related changes in OXTR and AVPRV1A binding in several

brain regions. Early separation disturbed the normal age-dependent shift in OXTR and AVPRV1A. OXTR binding was significantly lower in the agranular cortex (at juvenile and adolescent age), the lateral septum (at adult age) and the caudate putamen (at adult age), but higher in the medial preoptic area (at adolescent age) and ventromedial hypothalamus (at adult age) after exposure to MS (Lukas et al., 2010).

Ahern and Young (Heim et al., 2009) reported that parenting conditions in rats affected oxytocin content and dorsal raphe CRF2 densities in a sex-dependent manner; both measures were correlated with licking and grooming experienced during the first 10 days of life. Parenting conditions did not influence neuropeptide receptor densities in the ventral forebrain (Ahern and Young, 2009).

Intergenerational transmission of individual differences in stress-reactivity, possibly mediated in part by changes in oxytocin or its receptor, are likely candidates for some of the lasting effects of early experience (Bales et al., 2011). Early life experiences exert gender-dependent effects on the oxytocin and vasopressin systems, and stress reactivity (Carter et al., 2009), which are mediated through changes in expression of their central receptors.

Early social experiences may also induce epigenetic changes in the gene for the oxytocin receptor (Connelly, unpublished data). In rats maternal stimulation influences the maternal behaviour of female offspring, which appears to be related to OXTR gene expression (Champagne, 2008).

Epigenetic changes to the OXTR can also affect behaviour. Kumsta et al. (2013) reviewed the effects and causes of oxytocin receptor gene (OXTR) promoter methylation suggesting that psychosocial stress exposure might dynamically regulate OXTR in this manner to cause life-long changes in behaviour. Brüne (2012) discussed the impact of epigenetic changes but from an evolutionary perspective, emphasising the view that changes in the OXTR might not cause increased vulnerability to psychiatric disorders but differential susceptibility to the (early) environment.

#### 5.2.3. Childhood: stress, trauma and illness

Basal blood levels of oxytocin were reduced after childhood (but not adolescent) stress in a sample of healthy males (Opacka-Juffry and Mohiyeddini, 2012), while Heim et al. (2009) showed lower basal levels in the CSF of women who experienced child abuse (emotional abuse showed strongest effect). Reactivity of the oxytocin system was changed in response to the Trier social stress test in a sample of childhood cancer survivors compared to controls and people who had been sexually abused (Pierrehumbert et al., 2010). Although the sample in this study was not matched for age or socio-economic status, effects were detected when the analysis corrected for these.

A recent paper by Branchi et al. (2012), demonstrated a developmental role for peer interactions in the nest of rat pups. Individuals exposed to high levels of peer interactions in the nest showed enhanced adult affiliative behaviour and enhanced oxytocin receptor levels in selected nuclei of the amygdala as measured using autoradiography.

#### 5.2.4. Adolescence: experiences and drugs of abuse

In comparison to the large literature on early life, limited research has focussed on factors influencing the oxytocin system during adolescence. However, it is likely that this period marks a period of change in the oxytocin system based on the fact that the oxytocin interacts with so many systems that are either still developing during adolescence (for example, PFC) or that are experiencing a critical phase during adolescence (for example HPA axis; Tops et al., 2014-in this issue). It is likely that social experiences are able cause long-lasting effects. As detailed below, exposure to specific stimulants seems to induce transient increases in oxytocin (Dumont et al., 2009; Wolff et al., 2006). However, as Bowen et al. (2011) have shown in rats, a single administration of oxytocin during adolescence can have effects on behaviours such as alcohol drinking in adulthood. The mechanisms for such lasting effects of oxytocin exposure in adolescence remain to be explored. However, adolescent social experiences, such as peer interactions, that hold the potential to release endogenous oxytocin, also might have epigenetic consequences, possibly by sensitizing oxytocin pathways to respond more efficiently to oxytocin in adulthood.

In general, the existing literature suggests that social experience in early life can have life-long consequences for subsequent behaviour and emotional regulation. There also is increasing evidence that at alterations in oxytocin pathways, including the oxytocin and vasopressin peptides, and their receptors, may mediate these effects, possibly helping to account for individual differences in the vulnerability to substance abuse and addiction.

#### 5.2.5. Adulthood: reproductive behaviour, stress, drugs of abuse

Factors reported to influence the adult oxytocin system are, for example, strong natural triggers affecting homeostasis, stress and drugs of abuse. Even in adulthood, changes in oxytocin pathways can have profound and long-lasting consequences for behaviour.

For example, early research from Theodosis et al. (1986) showed that the adult nervous system can undergo significant experience-related structural changes throughout life. They showed that intracerebroventricular infusion of oxytocin, mimicking central release, induced neuronal-glial and synaptic changes in the SON similar to those detected under physiological stimulation. In 2010, Oliet and Bonfardin demonstrated anatomical plasticity in the SON of the hypothalamus during lactation, parturition and chronic dehydration. The structural plasticity of the hypothalamic magnocellular nuclei includes changes in neuron–glial interactions as well as changes in synaptic and extrasynaptic transmission of oxytocin and glutamate neurons. Additionally reproductive behaviour across the estrous cycle in female rats is influenced by dendritic remodelling in oxytocin neurons in the hypothalamic ventromedial nucleus (Ferri and Flanagan-Cato, 2012).

Stress is a natural trigger for oxytocin release, but a study by Unternaehrer et al. (2012) showed that even an experimental psychological stress situation was capable of causing alterations in methylation of the OXTR in humans. A Trier social stress test was capable of temporarily producing small but significant alterations in methylation of OXTR in mononuclear blood cells of middle-aged adults; methylation increased from pre- to post-stress and decreased from post-stress to follow-up. Whether these changes reflect responses to stress-related changes in oxytocin or are regulated by other pathways, such as changes in the HPA axis, remains to be studied.

The long-term effect of the exposure to drugs of abuse and alcohol is not clear yet. Oxytocin seems to be released in response after acute exposure to, for example, MDMA (ecstasy) and methamphetamine, as shown in human (Dumont et al., 2009; Wolff et al., 2006) and animal studies (Broadbear et al., 2011; Thompson et al., 2007). This could imply a role for oxytocin in some of the drug effects that are experienced. On the other hand, McGregor and Bowen (2012) shows that *chronic* drug use (e.g. cocaine, morphine and cannabis) and alcohol exposure decreases brain OXT synthesis in the rat. His group also did not show a significant difference in basal oxytocin (or vasopressin levels) in a group of current methamphetamine users meeting DSM IV criteria for dependence. However, these patients were not in a drug-free state (Carson et al., 2012).

### 5.3. Possible outcome of altered oxytocin levels and signalling

The long-term effect of social influences on brain structure and function including positive social experiences or adversity may be capable of affecting brain plasticity (Davidson and McEwen, 2012). The functioning of the oxytocin system seems to be sensitive to external influences such as epigenetic events and neuroplasticity (Macdonald, 2012; Meaney, 2001). Research shows that levels of oxytocin in the body differ depending on previous experiences, including endocrine experiences (Carter et al., 2009) and acute challenges (Ebstein et al., 2012; Feldman et al., 2010b; Grippo et al., 2009).

Looking at the functional effect of greater exposure to oxytocin during development in rats, data reports lower blood pressure (Holst et al., 2002), lower corticosterone levels (Sohlström et al., 2000), higher body weight (Sohlström et al., 2000), and oxytocin administration can reverse the effects of maternal malnutrition (Olausson et al., 2003). Importantly, a study by Bowen et al. (2011) demonstrated oxytocin administration during puberty included reduced alcohol drinking in adulthood.

Bales et al. (Bales et al., 2007) specifically investigated the long-term effects of increased oxytocin exposure in prairie voles, versus an oxytocin antagonist, or vehicle, on postnatal day 1. No significant treatment difference was observed for OXTR binding, however effects on the V1a receptor were found (some of which were gender specific).

Andersen (2003) reviewed the trajectories of brain development and discussed the windows in time during which brain development is most plastic, including age-related changes in neuron development and pruning, myelination, receptor and synapse and migration. Although oxytocin was not a specific focus of that paper, it is useful to note that developmental periods when the environment and epigenetics can have the strongest impact (for example, during gestation, after birth and in adolescence), are periods when it is likely that oxytocin is either elevated or otherwise in flux.

Influences during early development might affect migration and survival of neurons, which might strongly affect interactions between oxytocin and other neuromodulatory systems (as discussed in Section 6).

Prospective longitudinal studies are currently confirming that there are clear vulnerable periods. For example, Bosch and Neumann (2012) showed increased cortisol levels in teenagers who experienced prenatal stress, or those who experienced a combination of pre/postnatal adversity and adversity between age 6 and 11 (but not those with adversity between 0 and 5 only).

The previous section describes the individual differences that have been reported in the endogenous oxytocin, and the causes of these differences. The next paragraph will look at how oxytocin in general, and these individual differences in endogenous oxytocin, can affect susceptibility to addiction.

## 6. Oxytocin and addiction

Studies focused on the role of oxytocin on drug effects and addiction began to emerge in the early 1980s (for overview see Sarnyai and Kovacs, this issue). However, as more data on the functions of oxytocin has become available, theories and data on the role of oxytocin in addiction have begun to receive attention. New techniques and advances in research on the role of oxytocin in social rewards and on oxytocin as a treatment have put new life into the area.

Recent studies are also showing that oxytocin is released in response to, for example, acute MDMA (ecstasy) and methamphetamine administration both from human (Dumont et al., 2009; Wolff et al., 2006) and animal studies (Broadbear et al., 2011; Thompson et al., 2007). This could imply a role for oxytocin in some of the drug effects that are experienced.

In recent years, a large number of papers have reported oxytocin's direct and indirect effect on processes and behaviours linked to addiction, although few have looked at the role of individual differences in the endogenous oxytocin system on addiction directly. To examine the possible role of individual differences in the oxytocin system on addiction, this section will firstly describe the effects of oxytocin administration on drug use behaviour and secondly examine the neurobiological interactions that are at the basis of some of oxytocin's indirect effects on addictive behaviour. Table 1 provides an overview of the studies listing individual differences in the endogenous oxytocin system affecting alcohol and drug use; Table 2 provides an overview of the environmental factors reported to affect oxytocin in different life phases. It is postulated that differences in the endogenous oxytocin system will be able to affect both the initial response to drugs, and the chance addiction will develop (Section 7).

### 6.1. Direct effects of oxytocin on drug-taking behaviour and addiction

Over the years several effects of oxytocin on drug taking behaviour were demonstrated showing effects on various phases of drug use. Kovacs showed early on that centrally acting oxytocin inhibited the development of tolerance to morphine, and decreased the symptoms

**Table 1**
Overview of studies on individual differences in the endogenous oxytocin system. Outcomes are described in detail in the text in designated sections. Note: animal studies mainly relate to rodent studies.

| Factors | Outcome | Reference | Human/animal |
|---|---|---|---|
| *Individual factors* | | | |
| Species<br>Section 5.1 | Distributions of OXTR differ between species | Shapiro and Insel (1989),<br>Witt et al. (1992) | H/A |
| Gender<br>Section 5.1.1 | Sex steroids affect OXT synthesis and receptors | Gimpl and Fahrenholz (2001) | A |
| | OXTR expression is affected by oestrogen | Young et al. (1997) | A |
| | Oxytocin responses to stress sex dimorphic | Bales et al. (2011) | A |
| | Effect of prenatal stress and early life stress on the OXTR sex dimorphic | Carter et al. (2009) | A |
| | Effect steroid hormones and OXTR binding discussed | Opacka-Juffry and Mohiyeddini (2012) | H |
| Genetic differences<br>Section 5.1.2 | Structural and functional alterations in brain of OXTR risk allele (rs53576) carriers | Tost et al. (2010) | H |
| | OXT gene polymorphisms (rs4813625) influences dopamine function | Love et al. (2012) | H |
| | OXTR polymorphisms (rs4564970 and rs1488467) moderate alcohol induced aggressive behaviour in adult men | Johansson et al. (2012a, 2012b). | H |
| | Williams Syndrome: overproduction of oxytocin in response to specific stimuli | Dai et al. (2012) | H |
| | OXT levels reduced in children with autism | Hollander et al. (2003) | H |
| Age<br>Section 5.1.3 | Development OXT system starts in utero and continues into adolescence | Nylander and Roman (2012),<br>Bales and Perkeybile (2012) | H/A |
| | OXTR in the rat brain present during entire development; prairie voles show transient expression and reorganisation | Bales and Perkeybile (2012) | A |
| | OXTR density, but not receptor affinity changes in development | Bales and Perkeybile (2012) | A |
| Life phase<br>Section 5.2.5 | Lactation and parturition induce changes in synaptic and extrasynaptic transmission of oxytocin neurons in the SON of the hypothalamus | Oliet and Bonfardin (2010) | A |
| | Dendritic remodelling of OXT neurons in the hypothalamic ventromedial nucleus happens during the female cycle | Ferri and Flanagan-Cato (2012) | A |

**Table 2**
Overview of studies on environmental factors affecting in the endogenous oxytocin system in each life phase. Outcomes are described in detail in the text in designated sections. Note: animal studies mainly relate to rodent studies.

| Factors | Outcome | Reference | Human/animal |
|---|---|---|---|
| *Gestation* Section 5.2.1 | | | |
| Prenatal stress | Unpredictable stressors during last week of gestation resulted in reduced levels of OXT mRNA in the PVN and increased OXTR binding in the central amygdala in male rats | Lee et al. (2007) | A |
| | Restraint stress of dams in last week of gestation (plus parenting by these dams) caused decreased number of OXT-positive magnocellular neurons in male offspring | De Souza et al. (2013) | A |
| Prenatal drug exposure | Gestational cocaine exposure causes long-term decreases in OXT levels in hippocampus, hypothalamus and preoptic area | Johns et al. (1998) | A |
| | Combination of prenatal alcohol and nicotine exposure caused increased OXTR binding in the NAcc and hippocampus in adult males (not female) | Williams et al. (2009) | A |
| | Review: effect of prenatal cocaine exposure and maternal behaviour of cocaine-exposed dams on OXT levels and OXTR in neonatal rat pups | Williams and Johns (2014) | A |
| *Infancy and early life* Section 5.2.2 | | | |
| Social experiences and parenting | Infants exposed to high affect parent-infant synchrony had increased OXT saliva measures | Feldman et al. (2010a, 2010b) | H |
| | Secure attachment and oxytocin affect cortical loops | Tops et al. (2014-in this issue) | H |
| | Children raised in institutions in Romania before adoption showed altered oxytocin reactivity years later | Wismer Fries et al. (2005) | H |
| | Early parental separation was associated with decreased saliva cortisol excretion in response to intranasal oxytocin in young males | Meinlschmidt and Heim (2007) | H |
| | Early life stress (assessed by questionnaire) linked to lower OXT levels in healthy adult males | Opacka-Juffry and Mohiyeddini (2012) | H |
| | Review of early life manipulations on distribution and expression of OXTR | Veenema (2012) | A |
| | Altered levels of OXT after early-life stress in specific brain regions (e.g. hypothalamus, pituitary and amygdala) | Oreland et al. (2010) | A |
| | Maternal separation caused robust age-related changes in OXTR binding in several brain regions | Lukas et al. (2010) | A |
| | Parenting conditions in rats affected OT content in a sex dependent manner | Ahern and Young (2009) | A |
| | Maternal stimulation (grooming) appeared to affect oxytocin receptor gene expression | Champagne (2008) | A |
| *Childhood* Section 5.2.3 | | | |
| Stress | Basal blood levels of OXT were reduced after childhood (but not adolescent) stress in adult healthy males | Opacka-Juffry and Mohiyeddini (2012) | H |
| Trauma | Lower OXT basal levels in the CSF of women who experienced child abuse (emotional abuse strongest) | Heim et al. (2009) | H |
| Social environment | Enhanced oxytocin receptor levels in selected nuclei of the amygdala after high peer-interactions | Branchi et al. (2012) | A |
| Illness | Reactivity of OXT system was changed after Trier social stress test in childhood cancer survivors compared to controls and people who had been sexually abused | Pierrehumbert et al. (2010) | H |
| *Adolescence/Adulthood* Sections 5.2.4 & 5.2.5 | | | |
| Stress | Psychosocial stress exposure might dynamically regulate OXTR promoter methylation | Kumsta et al. (2013) | H |
| | Experimental psychological stress can induce transient alterations in methylation of the OXTR on mononuclear blood cells | Unternaehrer et al. (2012) | H |
| Drugs of abuse | Acute exposure to e.g. MDMA and methamphetamine cause OXT release | H: Dumont et al. (2009), Wolff et al. (2006), A: Broadbear et al. (2011), Thompson et al. (2007) | H/A |
| | Chronic drug use (e.g. cocaine, morphine and cannabis) and alcohol exposure decreases brain OXT synthesis | McGregor and Bowen (2012) | A |
| | No significant difference in basal oxytocin levels in a group of current methamphetamine users; note: users were not drug-free | Carson et al. (2012) | H |

of morphine withdrawal in mice, while reducing self-administration of heroin in rats (Ibragimov et al., 1987; Kovács et al., 1985, 1998).

Central oxytocin injections in animals were effective in modulating other drug-related behaviours. Intracerebroventricular (ICV) oxytocin inhibited methamphetamine-induced conditioned place preference (CPP), facilitated the extinction of methamphetamine-induced CPP and prevented its stress-induced reinstatement in mice (Qi et al., 2009). Additionally, microinjections of oxytocin directly into the NAcc core reduced the CPP produced by methamphetamine (as did injections into subthalamic nucleus), and inhibited cocaine-induced stereotyped behaviour in rats. (Baracz and Cornish, 2012; Sarnyai et al., 1991). Oxytocin was found to dose-dependently decrease cocaine-induced hyperlocomotion, and stereotyped grooming behaviour (Kovács et al., 1998).

Systemic administration of oxytocin was shown to have intrinsic reinforcing properties, and was able to affect drug-taking behaviour of drugs of abuse.

Liberzon et al. (1997) showed that oxytocin (subcutaneously 6 m/kg) itself could induce conditioned place preference and therefore has some motivational properties. Systemic administration of oxytocin reduced intravenous methamphetamine self-administration in rats (at 0.3–1 mg/kg i.p.; Carson et al., 2010a) and methamphetamine CPP rats (Baracz and Cornish, 2012). Oxytocin also diminished the capacity of non-contingent methamphetamine "primes" to reinstate methamphetamine-seeking behaviour in abstinent rats (Carson et al., 2010a). Oxytocin administration during adolescents (1 mg/kg i.p. PND 33–42) reduced alcohol consumption in adult rats (Bowen et al., 2011).

Looking at the underlying mechanisms behind these effects, Carson et al. (2010b) demonstrated that systemic oxytocin significantly reduced methamphetamine-induced neuronal activation in the NAcc core, and the subthalamic nucleus using Fos immunohistochemistry.

Interestingly, systemic oxytocin injections (2 mg/kg) strongly activated oxytocin-positive cells in the supraoptic nucleus (Carson et al., 2010a), supporting the hypothesis of a feed-forward effect of oxytocin

on its own dendritic release (Ludwig and Leng, 2006; Rossoni et al., 2008). Carson also hypothesized that there was a long-lasting up-regulation of endogenous oxytocinergic systems after repeated systemic oxytocin treatment to rats self-administering methamphetamine, since this resulted in chronically increased plasma levels of oxytocin (Carson et al., 2010a).

This overview suggests that oxytocin administered both centrally or in the peripherally can attenuate drug-taking behaviour in different phases of drug use.

### 6.2. Indirect effects of oxytocin on key systems involved in addiction

Mounting evidence demonstrates that neurobiological systems implicated in addiction processes (Section 3) interact with the oxytocin system. This section will explore the hypothesis that the endogenous oxytocin system is able to modulate drug taking and susceptibility to addiction via its effect on key biological systems such as the mesolimbic dopamine system, HPA-axis and immune system. (Several other interactions might be very important, but examining this is beyond the scope of this paper.) It is postulated that an underdeveloped oxytocin system is unable to modulate behaviour in a way that reduces, for example, the rewarding properties of drugs- and stress-induced relapse.

Fig. 2A shows the bidirectional interactions of oxytocin with key systems implicated in addiction focussing on neurotransmitter systems (e.g. dopamine and serotonin), the HPA-axis, the Vagal Nerve and glia. The feedback and feed-forward loops are suggested to fine tune the body's response to external challenges. Fig. 2B illustrates the situation in adults after a less optimal development of the bidirectional interactions with oxytocin system. The oxytocin system is not as able to dampen the response to stressors and drugs of abuse, leaving the body more prone to develop maladaptive behaviour such as excessive alcohol and drug use. The following sections will discuss these interactions and the effect of environment on them in detail.

#### 6.2.1. Oxytocin interactions with the mesolimbic dopamine system

Nearly all drugs of abuse increase dopamine in the mesolimbic dopamine system, either directly or indirectly (Pierce and Kumaresan, 2006). Thomas Insel and others have commented on the fact that the dopamine reward pathway seems to be involved in parenting and social reward (Insel, 2003) and have speculated on the shared neurobiological basis with addiction. Recent studies show that the oxytocin and dopamine systems interact to affect the rewarding value of social stimuli (Champagne et al., 2004; Shahrokh et al. (2010) and drug reward (Young et al., 2008, 2011). This interaction has been demonstrated in, for example, the VTA and NAcc, and research is now focusing on the PFC. An interaction between the dopamine and oxytocin system could be a driving force behind the balance between social and drugs reward. Two recent papers by Tops et al. (2013, 2014-in this issue) explore experience-dependent plasticity, where the parent's behaviour affects the brain development of the child. We postulate that attachment and oxytocin affect engagement of corticostriatal loops, thus affecting the balance between the search for immediate reward and familiarity (Tops et al., 2013, 2014-in this issue).

Several studies using prairie voles have illustrated the link between oxytocin and dopamine involvement in the regulation of social behaviour, and in the effects of exposure to parental behaviour. Shahrokh et al. (2010) have provided comprehensive novel evidence for a direct effect of oxytocin at the level of the VTA in the regulation of NAcc dopamine levels from studies of maternal behaviour in lactating rats. Individual differences in maternal care (e.g. licking and grooming) can be regulated either with oxytocin antagonists, or treatments that eliminate differences in the NAcc dopamine signal.

Direct infusion of oxytocin into the VTA increased the dopamine signal in the NAcc (Shahrokh et al., 2010). High LG compared with low LG mothers showed greater increases in dopamine signal in the NAcc during bouts of pup LG. Importantly, this difference was abolished after infusion of an oxytocin receptor antagonist directly into the VTA (Shahrokh et al., 2010).

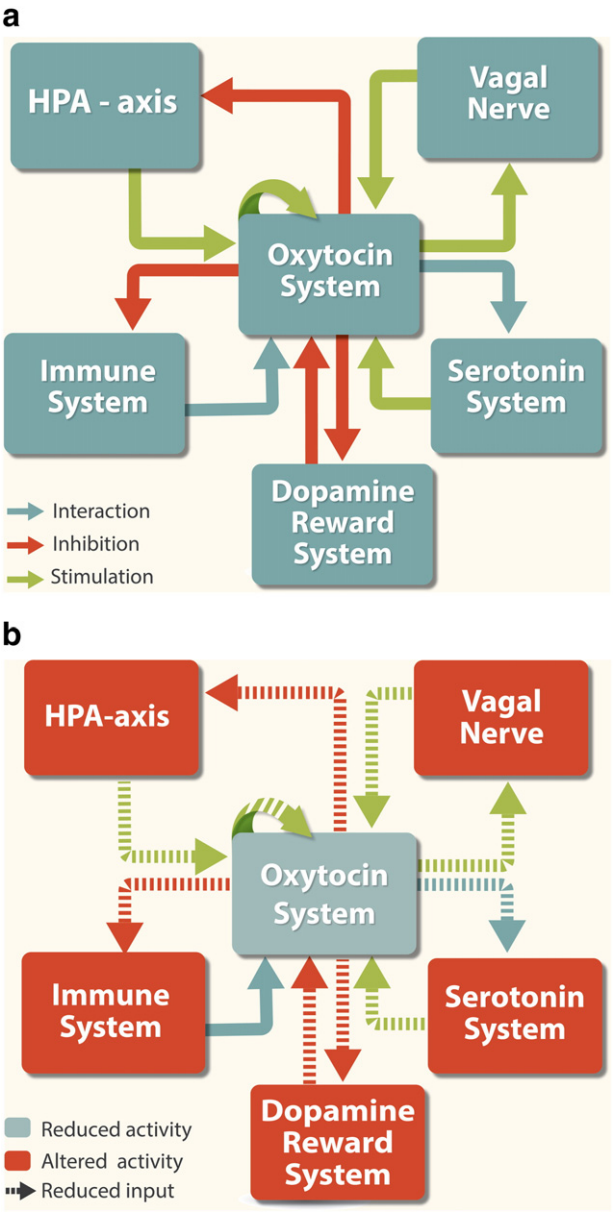


**Fig. 2.** Bi-directional interactions between oxytocin and key systems implicated in addiction. Oxytocin has bidirectional interactions with several systems linked to direct drug effects and increased susceptibility to addiction. Fig. 2A shows several key interactions in an individual with an oxytocin system that has developed fully. Arrows show the type of interaction (blue for an interaction; red for inhibitory, green for stimulation). This graph is a simplified representation of the situation since more interactions exist and the systems also interact with each other. Fig. 2B shows the suggested situation after suboptimal development of the oxytocin system due to early adversity. Each of the systems will be affected by early adversity (red and light blue boxes). Additionally, the modulatory role of oxytocin on the other systems is reduced (dashed lines). It is proposed that oxytocin levels and reactivity will be reduced and that the negative feedback loops that would normally exist might not work optimally. The suggested outcome is an increased susceptibility to addiction.

Interestingly, Young et al. (2008, 2011) provided further evidence demonstrating the interactions between the oxytocin and dopamine system in both social and drug reward in prairie voles: methamphetamine was shown to reduce pair bonding and pair bonding was able to reduce the rewarding properties of methamphetamine in prairie voles. The mesolimbic dopamine pathway and oxytocin were the key regulators of this behaviour, interacting in the NAcc. They showed that

drugs in prairie voles could reduce the dopamine release after social interaction, and that social interaction could reduce the reward from drugs. Unpublished data by Wang also demonstrated that prefrontal oxytocin mediates drug and social reward interaction. Local administration of oxytocin in this area can restore drug-induced alterations in pair bonding.

These data from animal studies show that the dopamine and oxytocin system are not just co-localised, or have a unidirectional effect, but rather the interactions among oxytocin and dopamine are bidirectional.

From other basic research we also know that oxytocin acts on oxytocin receptors in the medial preoptic area resulting in an increased dopamine release in the VTA (Champagne et al., 2004; Shahrokh et al., 2010). Infusing an oxytocin receptor antagonist in the VTA diminishes this effect completely (Shahrokh et al., 2010) and even results in a functional normalisation of maternal behaviour in female rats that naturally show reduced levels of pup LG (Champagne et al., 2004).

The existence of a dopamine-oxytocin interaction may not be surprising, since early studies by Kovacs et al. (for a review see Sarnyai and Kovacs, this issue) showed that the rewarding effect of drugs like methamphetamine and cocaine could be modulated using oxytocin. The new studies however demonstrate the direct functional bidirectional interaction between the dopamine and oxytocin system and the effects this interaction has on social and drug-taking behaviour.

However, we know that the oxytocin system shows large interspecies differences, so the next question would be: does this interaction also exist in humans as well. Interestingly, Love et al. (2012) have recently shown that oxytocin gene polymorphisms in humans influence dopamine function in a gender-specific manner.

*6.2.2. Interactions with the HPA-axis*

Oxytocin has a bidirectional interaction with the HPA-axis. Stressors, such as a Trier social stress task, can induce changes in oxytocin levels in humans (Pierrehumbert et al., 2010). Additionally, oxytocin tends to reduce ACTH secretion from the anterior pituitary (Opacka-Juffry and Mohiyeddini, 2012) as reported in humans, and may tonically inhibit CRF, and, consequently, corticosterone secretion in virgin female rats (Neumann et al., 2000).

CRF is distributed throughout the brain but particularly high concentrations of cell bodies are found in the PVN of the hypothalamus. Dabrowska et al. (2011) provided neuroanatomical evidence in rats for a possible reciprocal regulation of the CRF family of peptides, as well as oxytocin systems in the hypothalamus and the BNST. CRFR2 located on oxytocinergic neurons and axon terminals might regulate the release of this neuropeptide and OXTR activation might regulate excitability of CRF neurons in the PVN. This might be a crucial part of potential feedback loop between the hypothalamic oxytocin system and the forebrain CRF system that could significantly impact affective and social behaviours, in particular during times of stress.

Koob (Koob, 2008; Koob and Volkow, 2009) reviews evidence demonstrating a strong role for CRF in addiction, including in the transition to dependence and the maintenance of dependence. Oxytocin can modulate responsiveness of the HPA axis (Baskerville and Douglas, 2010; Parker et al., 2005). At a behavioural level: oxytocin can protect against some of the effects of social stress and isolation in animals (Parker et al., 2005). Thus, oxytocin may be perceived as a common regulatory element of the social environment, stress response, and stress-induced risks on mental and physical health (Smith and Wang, 2012).

*6.2.3. Interactions with serotonin*

Serotonin and its interaction with oxytocin seem to be important in specific drug effects, such as seen after MDMA use in animals and humans. This is the primary focus of a different review paper in this issue (Broadbear et al., 2011; 2013). Importantly, Eaton et al. (2012) demonstrated that oxytocin has site-specific organisational influence on the serotonin system during the neonatal period. For example agonist treatment on PND 1 affected serotonin axon length density on PND 21 in regions of the hypothalamus (but not PVN) and amygdala. These effects for example modulated social behaviour in prairie voles. It is not clear whether these influences have functional outcomes on addiction-related behaviours.

*6.2.4. Interactions with glia and the peripheral immune system*

A primed immune system seems to increase the susceptibility to develop addiction as well as other mental health problems (Frank et al., 2011). Several triggers can cause this primed state to develop (for example, trauma and illness).

Oxytocin seems to interact with the peripheral immune system, where oxytocin has an anti-inflammatory effect (Gutkowska and Jankowski, 2012). Interestingly Clodi et al. (2008) demonstrated that exogenous oxytocin could reduce the neuroendocrine and cytokine response to bacterial endotoxin in healthy men.

The interaction between oxytocin and glia is also of interest in the suggested tripartide synapse. The PVN of the hypothalamus acts as an integrative centre (Yang et al., 1997): in this area glia are able to modulate glutamate/GABA and oxytocin neurotransmission in an environment-dependent manner. Oxytocin neurons in the PVN (and SON) are surrounded by glia in a dynamic interaction in a tripartide synapse (Theodosis et al., 2008). This allows not only rapid adjustment to the changing environment (for example, stress) but also to longer term changes, such as during pregnancy. Oliet et al. (2008) showed how glial processes change shape, by protruding and becoming a barrier that limits diffusion of neurotransmitters, or alternatively retracting to allow the release of neurotransmitters. This structural change directly affects glutamate and GABA neurotransmission, as well as neurotransmission in the oxytocin neurons. Additionally, changes in the glutamate system are often reported after, for example, maternal separation and have been linked to changes in the psychological aspects of drug-taking behaviour. A recent review also demonstrates important interactions among dopamine, glutamate and oxytocin (Yang et al., 2010).

*6.2.5. Interactions with the vagus nerve*

The autonomic nervous system helps to regulate the emotional and subjective experiences that are associated with addiction. The parasympathetic or vagal branch of the autonomic nervous system is of particular importance to the capacity to modulate over-reactivity to challenges, including those associated with addiction and withdrawal. The brainstem regions that regulate the efferent vagus can be divided into two phylogenetically and anatomically distinct systems. The older unmyelinated vagal pathways originate in the dorsal motor complex, while the more recent myelinated fibres (primarily found in mammals) can be traced to the ventral vagal complex (Porges, 2007). Myelinated vagal pathways constitute the social engagement system, which coordinates autonomic activities need to support social communication and emotional regulation. Research directly examining the role of the parasympathetic processes in addiction is comparatively rare. However, as one example, Liu et al. (2011) recently showed that vagal nerve stimulation can inhibit heroin- or heroin cue-induced relapse in rats, in part by regulation of the nucleus accumbens. Indirect evidence for a role for the vagus in addiction comes from mounting evidence for a role for the vagus in the regulation of social behaviour (Porges, 2007).

Both social behaviour and activity of the vagus can be modulated by oxytocin (Carter et al., 2009). In addition, the visceral tissues that are outside of the blood brain barrier (including the vagus nerve) contain oxytocin receptors, (Welch et al., 2009). Thus, the effects of oxytocin may be readily and quickly transmitted to the central nervous system via the vagus nerve. The sensitivity of the autonomic nervous system to the regulatory effects of oxytocin may help to explain recent data implicating oxytocin in the vulnerability to addiction and the capacity to manage the symptoms of withdrawal (Pedersen et al., 2012).

### 6.3. Localisation of interactions

The interactions described above are believed to take place primarily in the hypothalamus and in areas important in the mesolimbic dopamine system (such as VTA, NAcc and PFC) as well as in the periphery. The hypothalamus is an interesting area as it is a meeting place for several important regulatory systems including oxytocin, serotonin and GABA/glutamate neurons, HPA-axis, information from the spinal cord, and the immune system (Eaton et al., 2012; Oliet et al., 2008; Yang et al., 1997). These interconnections could be key in modulating our vulnerability to develop neuropsychiatric disorders and addiction. Several studies have shown long-term, experienced-based changes to the HPA axis and hypothalamus (Davidson and McEwen, 2012).

## 7. Summary of the suggested model

The oxytocin system changes and matures over time as part of normal development (Section 5.1.3). This paper postulates that early external influences (like stress, social adversity and infection) affect the developing endogenous oxytocin system, changing receptors, hardware and set points. This results in individual differences in oxytocin levels, and altered responsiveness of the oxytocin system. This disturbed development can lead to increased susceptibility to the development of addiction, and reduced resilience to stress.

Early influences also affect the other systems that the oxytocin system interacts with, such as neurotransmitter systems (like dopamine, serotonin, glutamate and GABA), the immune system, and the stress axis (Fig. 2). Specific sensitive periods exist for all these systems where external influences can have long-lasting effects, for example during gestation and after birth, but also during adolescence. Individuals may show only minor differences in behaviour and function unless subsequent stressors, infection, or drug use, challenges the system again. This is when the increased susceptibility to addiction becomes apparent. Since these systems are all inter-dependent and regulate each other, early life adversity can change the balance of this entire system and minimise the negative feedback loops that would normally exist.

It is postulated that early adversity can disrupt the normal development of the oxytocin system and other systems, leading to a less fine-tuned system. A well-developed oxytocin system is in a position to directly and indirectly increase resilience, for example by reducing drug reward, increasing social reward, reducing anxiety, reducing stress response and immune stimulation. A well-developed system that is able to respond in times of stress, as well as social support, may decrease the chance that someone escalates their use and relapses when they have attempted to quit. If adversity is encountered, the oxytocin system still develops, but basal levels might be lower and it might be less responsive. Connectivity might be different with other systems. In short, individual differences in the endogenous oxytocin system may arise based on early life experiences.

## 8. Discussion: limitations and considerations

Here we propose a framework, focused on contemporary knowledge of oxytocin, for future research on drug addiction. Our goal is to generate hypotheses on the role of the endogenous oxytocin system in addiction. There is at present no direct evidence of the role of the endogenous oxytocin in addiction in humans. However, research in this area is progressing rapidly. The following considerations and limitations are important around this theory.

The paper has not focussed extensively on examining the role of prenatal drug use on the oxytocin system or subsequent drug use. The pharmacological effects of drugs of course add further complexity to our framework. However, a review by Williams and Johns (2014) explores this relationship in detail.

Studying the neurobiology of addiction involves many inter-dependent systems. This makes it hard to comprehend the effect of a change in the oxytocin system and pinpointing whether it leads to functional changes. Compensation by other systems is always a possibility. Additionally, changes as a result of early adversity are not exclusive to addiction. The systems that are affected by an altered oxytocin system have functions in many other tasks such as learning and memory, mood, pain, social behaviour and so forth (Carter et al., 2009; Opacka-Juffry and Mohiyeddini, 2012).

Sex-dependent differences have been reported in the oxytocin system, and the effect of stress on the oxytocin system (Section 5.1.1) However, most preclinical addiction studies use males. The gender differences in the endogenous oxytocin system in males and females might warrant a more comprehensive approach. Especially since humans also show a gender difference in problematic drug use, which varies across different phases of addiction (Becker and Hu, 2008). Females begin regularly self-administering licit and illicit drugs of abuse at lower doses than do males, but use escalates more rapidly to addiction. Additionally, females are at greater risk for relapse following abstinence (for a review see Becker and Hu, 2008). It might be that the oxytocin system has a stronger influence on drug-taking behaviour in women.

While describing the effects of oxytocin on addiction, vasopressin has been partly disregarded. However, oxytocin and vasopressin show cross reactivity and both are altered after, for example, maternal separation (Carter et al., 2009; Lukas et al., 2010). Early studies examined both the effects of oxytocin and vasopressin on behaviour, with these neuropeptides showing opposing effects on tolerance and withdrawal of, for example, ethanol, heroin and cocaine (Sarnyai, 1998; Sarnyai et al., 1992; Szabó et al., 1987, 1988). However, most recent studies only focus on one of the two peptides. Edwards (Edwards et al., 2012) has suggested vasopressin may be important in addiction through its affects on the brain stress-system. This recent study demonstrated the role of vasopressin AVPRV1b receptors in mediating the transition to excessive drinking in ethanol-dependent rats. Early life stress might cause changes in the vasopressin system of men, with most research focusing on AVPRV1b receptor.

Oxytocin seems to increase sensitivity to social cues (Guastella et al., 2012). A strong social network and strong relations have been known to delay initiation of drug use and have a positive effect on treatment outcome when dependence has developed. Adolescence is characterised by an increased sensitivity to peers and social pressure and peer pressure or encouragement can contribute to drug use, whether positive or negative, with effects that are most apparent for the initiation of use (Mundt, 2011). Increased oxytocin levels might further increase the rewarding value that is received from social interactions and may make young people very sensitive to peer pressure. Peer culture around low or moderate use can be protective against excessive use; however this is not commonplace in all cultures.

Lastly, this theory might seem to imply that having more oxytocin is regarded as optimal. However, genetic disorders like Williams Syndrome show that high levels of oxytocin do not necessarily promote optimal behavioural responses (Dai et al., 2012). As another example, an exaggerated oxytocin release in response to stress (or cortisol administration) may be maladaptive or indicative of a particularly intense form of stress (Pierrehumbert et al., 2010). A well-regulated system with well functioning feedback loops is likely to be ideal. However, circumstances that block these natural systems from developing normally tend to disrupt natural feedback systems, creating complex disorders with negative behavioural

and physiological consequences. Understanding the role of individual differences in alcohol and drug use and the development of dependence can open new opportunities for the development of valid therapeutic approaches to drug addiction.

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