Published in final edited form as:
Behav Pharmacol. 2014 September ; 25(5 0 6): 445–457. doi:10.1097/FBP.0000000000000049.

Stress, gender, and addiction: potential roles of CRF, oxytocin and argininevasopressin

Verónica Bisagno, PhD[1] and **Jean Lud Cadet, MD.**[2]

[1] Instituto de Investigaciones Farmacológicas (ININFA-UBA-CONICET), Junín 956, piso 5, C1113-Buenos Aires, Argentina. Phone: (+54-11) 4961-6784, Fax: (+54-11) 4963-8593

[2] NIDA Intramural Program, Molecular Neuropsychiatry Research Branch. 251 Bayview Boulevard, Baltimore, MD 21224, USA.

Abstract

Stress sensitivity and gender are predictive factors for the development of neuropsychiatric disorders. Life stresses are not only risk factors for the development of addiction but they are also triggers for relapse to drug use. Therefore, it is imperative to elucidate the molecular mechanisms underlying the interactions between stress and drug abuse, because this understanding may help in the development of novel and more effective therapeutic approaches to block the clinical manifestations of drug addiction. The development and clinical course of addiction-related disorders do appear to involve neuroadaptations within neurocircuitries that modulate stress responses and are influenced by several neuropeptides. These include corticotropin releasing factor (CRF), the prototypic member of this class, as well as oxytocin (OXY) and arginine-vasopressin (AVP) that play important roles in affiliative behaviors. Interestingly, these peptides function to balance emotional behaviors in a sexual dimorphism of OXY/AVP systems, a fact that might play an important role in the differential responses of women and men to stressful stimuli and the specific gender-based prevalence of certain addictive disorders. Thus, this review aims to summarize (1) the contribution of sex differences to the function of dopamine systems, and (2) the behavioral, neurochemical, and anatomical changes in brain stress systems.

Keywords

stress; addiction; gender; CRF; oxytocin; arginine-vasopressin

INTRODUCTION

A dynamic interplay of genetic, epigenetic, and environmental factors orchestrates individual differences in the etiology and clinical manifestations of anxiety- and stress-related disorders. Stress is associated with the development of neuropsychiatric conditions and influences the development and progression of some neuropsychiatric disorders

Correspondence: Jean Lud Cadet MD, Chief, Molecular Neuropsychiatry Research Branch, Intramural Research Program, NIDA/NIH/DHHS, 251 Bayview Boulevard, Baltimore, MD 21224, USA, jcadet@intra.nida.nih.gov, Tel: 443-740-2656, Fax: 443-740-2856..

The authors declare that they do not have any conflicts of interest (financial or otherwise) related to the content of this manuscript.

(Sapolsky, 2000; Karatsoreos and McEwen, 2011). Life stress events are not only risk factors for the development of addiction but they can also trigger relapse to drug taking and the associated adverse consequences of drug use.

Addictive disorders are chronic diseases of brain reward, motivation, and memory circuits (Volkow et al., 2012). Dysfunctions within these brain circuits are associated with characteristic biopsychosocial manifestations of addiction. Those include inability to abstain from drug seeking and taking, unbearable craving, and behavioral impairments of various kinds such as the inability to recognize the deterioration of interpersonal relationships (Volkow et al., 2012). The addicted state is also accompanied by repeated cycles of remissions and relapses that are associated with adverse neuropsychiatric consequences including depression and psychotic episodes, depending on the primary drug of choice (Wilson and Cadet, 2009). Moreover, addictive behaviors are associated with specific cognitive disturbances and neuroimaging evidence for brain dysfunctions in a diverse population of drug addicts. Postmortem studies have also revealed biochemical and/or structural abnormalities in some addicted individuals (Cadet et al., 2014).

The biochemical and pharmacological effects of licit and illicit drugs are necessary but they are not sufficient for the development and the maintenance of addicted states (Flagel et al., 2009; Piazza and Deroche-Gamonet, 2013). Other modulating factors include access to drugs, genetic predisposition, psychosocial stressors, and psychiatric co-morbid states (Volkow et al., 2011; Post and Kalivas, 2013). Individuals exposed to chronic stress exhibit a higher propensity to become drug addicts or alcoholics (Sinha, 2008). Both drug addiction and stress-related disorders are also characterized by profound gender differences (Kuhn et al., 2010; Donner and Lowry, 2013). Many sexually dimorphic characteristics, including neurotransmitter systems (Valentino and Van Bockstaele, 2008), actions of reproductive steroid hormones within the mesolimbic and mesocortical systems (Weiser et al., 2008), neuroactive peptides (Bangasser et al., 2010), and epigenetic regulation of gene expression (Hoffmann and Spengler, 2012), have emerged as potential candidates for explaining sexually dimorphic neuropsychiatric disorders. The discussion of all these factors is beyond the scope of this review, and the reader is therefore referred to the reviews referenced above. The present review will focus on integrating data on the interactions of brain stress and reward systems that seem to play key roles in mediating the appearance of addiction and in influencing the clinical course of these disorders. To that end, we will discuss preclinical and clinical data on the effects of addiction on the expression and/or levels of corticotropin releasing factor (CRF), oxytocin (OXY) and arginine-vasopressin (AVP). We will also discussion their potential influence on the clinical course of addiction.

Sex differences in the epidemiology of addiction and other neuropsychiatric disorders

Epidemiological studies have observed significant gender-specific differences among patients suffering from addiction and other neuropsychiatric disorders (Parker and Brotchie, 2010; Hudson and Stamp, 2011). The US National Institute of Mental Health has reported that the lifetime prevalence of an anxiety disorder is 60% higher in women than in men (McLean and Anderson, 2009). The onset, severity, clinical course, and treatment response of anxiety disorders also differ significantly in women (Pigott, 2003). Importantly, the

gender bias in neuropsychiatric disorders, including post-traumatic stress disorder (PTSD), remains even after adjusting for the type of trauma, preexisting psychiatric disorders, and sex differences in reporting (Breslau et al., 1999; Tolin and Foa, 2006). Several studies have found increased prevalence of depression in women (Weissman et al., 1993; Kendler et al., 2000). The USNational Co-morbidity Survey Replication (NCS-R) study that surveyed over 9000 English-speaking respondents, found that the lifetime risk of 'any mood disorder' was 1.5 times higher for women (Kessler et al., 2005). Similar gender differences exist for addictive disorders. For example, more adult males abuse addictive drugs than females across most drug classes, including alcohol, psychostimulants and narcotics (Tetrault et al., 2008). However, women develop addiction more quickly (Anker and Carroll, 2010). There are also critical differences in the way that illicit substances affect the two sexes. For example, in comparison to men, women begin using drugs younger; enter into drug rehabilitation sooner, and experience shorter periods of drug abstinence (Brady and Randall, 1999). Moreover, female injection drug users (IDU) are more likely to engage in risky behaviors than male IDU (Evans et al., 2003). Men and women also show different propensities to relapse, and are differentially affected by triggers for relapse to drug taking, putting women at greater risk for repeated relapses (Kosten et al., 1993; Becker and Hu, 2008) in spite of the higher prevalence of drug abuse in men (Brady and Randall, 1999). Interestingly, once the addiction cycle resumes, women show longer periods of drug use before their next quit attempt (Gallop et al., 2007).

In general, women appear to be more sensitive to cocaine abuse (Kosten et al., 1993). For example, women initiate cocaine uses sooner, take less time than men to become dependent (Lex, 1991), abuse cocaine more frequently, and remain abstinent for shorter periods of time (Griffin et al., 1989). Female cocaine abusers tend to be more affected by drug-related cues (Robbins et al., 1999; Lynch et al., 2002), and cocaine-associated paraphernalia induce stronger craving in women than in men (Elman et al., 2001).

Potential mechanisms for gender differences in drug addiction

A number of reports have provided support for the notion that sex differences in stress and emotionality may be responsible for the higher relapse risk seen in women. Negative affective states precede drug-taking behaviors, especially in women (Zilberman et al., 2003). Carroll et al. (2004) reported that relapse to smoking, alcohol, and cocaine use was more strongly linked to stress and depression in women than in men. A recent study by Potenza et al. (2012) of neural correlates of cue-induced craving states in women and men addicted to cocaine reported sex differences in cue-induced craving, with corticostriatal-limbic hyperactivity being linked to stress cues in women but to drug cues in men (Potenza et al., 2012).

The gender differences may also be a result of hormonal and neural differences between men and women in relationship to their response to these drugs (Kuhn et al., 2010). For example, women experience greater positive effects from drugs during the follicular phase of their menstrual cycle, when circulating gonadal hormones are highest (Evans et al., 2002). Also, in women, surges of estrogen are associated with increased dopamine activity (DiPaolo et al, 1988; Levesque et al, 1989). In contrast, progesterone has an overall blunting

effect on the striatal dopamine system, opposing the actions of estradiol (Fernandez-Ruiz et al, 1990; White et al, 2002). In fact, progesterone administration to men dampens subjective and physiological responses to cocaine (Sofuoglu et al., 2004). It has been posited that the ratio of estrogen to progesterone, which changes throughout the menstrual cycle, helps determine responsiveness to amphetamine (White et al., 2002).

In addition to gender differences in cocaine addiction, women have been reported to be more dependent on methamphetamine (METH), find METH more appealing, and prefer this psychostimulant (Dluzen and Liu, 2008). Women also exhibit higher comorbid neuropsychiatric disorders and suicidal tendencies than their male counterparts (Hser et al., 2005) and prefer METH to other drugs, while men will use an alternative drug if METH is unavailable (Brecht et al., 2004). Regardless of menstrual phase differences, however, women showed less striatal amphetamine-induced dopamine release than men (Munro et al., 2006).

Animal models of cocaine addiction have confirmed clinical findings of important sex differences in effects of cocaine and amphetamine, as female rats significantly differ from males in several aspects of addiction to psychostimulants. For example, during short access, fixed-ratio responding, females and males self-administer comparable amounts of cocaine (Caine et al., 2004), but females will work harder for psychostimulants under a progressive ratio, escalate use faster, and bar press more during extinction than males (Lynch et al., 2002; 2006; Quiñones-Jenab, 2006). The latter findings have been interpreted to indicate that motivation to take drugs is stronger in females. It has also been shown that estrogen has facilitatory effects on cocaine-induced locomotor and self-administration behaviors (Lynch et al., 2002; Festa and Quinones-Jenab, 2004; Quinones-Jenab, 2006; Becker and Hu, 2008). Nevertheless, progesterone administration was reported to inhibit cocaine-induced conditioned place preference (CPP) (Russo et al., 2003). Progesterone administration also reduced the acquisition (Jackson et al., 2006) and escalation (Larson et al., 2007) phases of cocaine self-administration, further suggesting that progesterone might reduce craving for cocaine. Anker et al., (2007) corroborated this idea by demonstrating that progesterone decreased cocaine-primed reinstatement in females. In addition, progesterone counteracted the facilitatory effects of estrogen on cocaine self-administration in gonadectomized rats (Jackson et al., 2006). Sofuoglu et al., (2004) reported that progesterone also attenuated some of the subjective effects of cocaine. The dynamics of estrogen–progesterone interactions affecting behavioral responses to cocaine may have physiological relevance. For example, because serum levels of progesterone and estrogen are constantly changing in females, it is feasible that hormonal profiles may ultimately affect a female's behavioral and subjective responses to cocaine. Preclinical and clinical studies directly demonstrate that progesterone is an important contributor to sex differences in response to cocaine. Moreover, most studies suggest that administration of progesterone consistently inhibits or attenuates the subjective and reward effects of .cocaine. In addition to their responses to cocaine, female rodents have greater sensitivity than males to METH-induced motor stimulating effects (Schindler et al., 2002). Also, female rats also experience greater sensitivity than males to the reinforcing effects of daily METH, as evidenced by greater escalation of METH intake and seeking (Reichel et al., 2012; Roth and Carroll, 2004).

In summary, preclinical research has revealed that locomotor stimulation and acquisition of self-administration of psychostimulants occur at lower doses and may be of greater magnitude in females than in males (Khun et al., 2010). Importantly, differences in vulnerability to relapse and reinstatement are prominent in female rodents across the ovarian cycle (Lynch et al., 2002), suggesting an important role of ovarian hormones in influencing susceptibility to drug abuse and addiction.

Addiction and the neurobiology of stress systems

Individuals exposed to chronic stress exhibit a higher propensity to become drug addicts. For example, abuse rates in combat veterans suffering from PTSD are significantly higher than those veterans without PTSD (McFall et al., 1992; Ouimette et al., 2007). Stress-induced relapse is also higher in PTSD patients. In general, there is a higher prevalence of addiction in patients diagnosed with anxiety disorders and depression (Ford et al., 2009). Additionally, childhood trauma is associated with increase vulnerability to addiction (Triffleman et al., 1995). Exposure to high peer deviance in childhood and adolescence is among the strongest known risk factors for drug use and drug abuse (Andrews et al., 2002). Interestingly, a very receny study has found that individuals with increased risks of drug addiction because of parental divorce or genetic liability are more sensitive to the pathogenic effects of peer deviance (Kendler et al., 2014).

Stress and addiction are interconnected in several ways. For example, stressful life events may predispose individuals to engage in addictive behavior and/or relapse (Sinha, 2008). Excessive drug taking might cause early activation of the the HPA response, followed by sensitization of extrahypothalamic CRF systems (Koob and Kreek, 2007). Human polysubstance users do indeed show blunted ACTH and cortisol responses to CRH administration, which are signs of disturbed HPA regulation (Contoreggi et al., 2003). . The finding of an activated HPA axis in this population suggested an overlapping role of central CRH and HPA axis activation in affective disorders and substance abuse (Contoreggi et al., 2003). Interestingly, stress is reinforcing in certain contexts but can also work to suppress the reward value of some reinforcers (Koob et al., 2014).

The neural circuitry underlying responses to stress clearly interdigitate with other systems that promote drug reward. Functional magnetic resonance imaging (fMRI) studies have indicated that stress and drug exposure can activate similar brain regions, including mesolimbic and mesocortical dopamine projection regions (Kufahl et al., 2005; Sinha and Li, 2007). Both stress and drug exposure can increase mesolimbic dopamine transmission (Di Chiara and Imperato 1988; Abercrombie et al. 1989). Additionally, acute drug administration and acute stress exposure elicit a similar enhancement of excitatory synaptic strength in the ventral tegmental area (VTA), strengthening the claim that these stimuli activate similar circuits (Saal et al., 2003). Within this circuitry a key projection from the central amygdala to the bed nucleus of the stria terminalis (BNST) is critically involved in the ability of stress to modulate drug reward (Erb and Stewart, 1999; Erb et al., 2001). Dopaminergic systems have important connections with neuroendocrine stress systems in the hypothalamus, hippocampus, nucleus accumbens and the amygdala (Koob et al., 2014).

To determine whether stress is a casual factor in the development of addiction, animal models have been used to evaluate the interaction between stress and drug addiction. Behavioral responses to cocaine, amphetamine and morphine, including locomotor activity and stereotypy, are enhanced following stress (MacLennan and Maier, 1983; Antelman et al., 1980; Leyton and Stewart, 1990). Additionally, stress leads to a potentiation of cocaine-induced extracellular dopamine levels and of amphetamine-induced striatal dopamine release (Sorg and Kalivas, 1993; Pacchioni et al., 2002). Repeated stress exposure has also been shown to facilitate acquisition of drug self-administration (Piazza et al., 1989; Haney et al., 1995) and drug CPP (McLaughlin et al., 2006; Der-Avakian et al., 2007). Conversely, both repeated and acute drug administration can lead to sensitized behavioral and neurochemical responses to stress: behaviors such as freezing in response to shock and anorexia in response to mild tail pinch are increased in drug-experienced animals (Antelman et al., 1980; Hamamura and Fibiger, 1993). Furthermore, chronic drug exposure leads to enhanced dopamine metabolism in the prefrontal cortex and nucleus accumbens in response to footshock stress, as well an enhanced dopamine release in the medial prefrontal cortex (Kalivas and Duffy, 1989; Hamamura and Fibiger, 1993). Foot-shock leads to reinstatement of previously extinguished operant responding for drug self-administration (Shaham et al., 1996; Ahmed and Koob, 1997). Other stressors such as tail pinch, and forced swim stress have also been shown to reactivate drug CPP (Sanchez et al., 2003; Kreibich and Blendy, 2004). Taken together, animal studies have revealed enhancement of drug self-administration and reinstatement to drug seeking by stress exposure (Koob et al., 2014). These effects might be secondary to stress-induced physiological, neurochemical, and behavioral alterations that impact systems that are also affected by drugs of abuse, which could work coincidently to negatively impact craving and compulsive seeking, to maintain drug use, and to promote relapse (Sinha, 2008). These behaviors might be related to interactions of the dopaminergic systems with specific neuropeptides including CRF, OXY, and vasopressin. In the following sections, we discuss the potential gender-specific role of these peptides in addiction.

CRF and neuropsychiatry

CRF is a 41amino acid-containing neuropeptide that was discovered by Vale in 1981 (Vale, 1981). CRF orchestrates the stress response by acting at the level of the pituitary to initiate the hypothalamic-pituitary-adrenal (HPA) axis response to stress, as well as centrally to modulate limbic and brain monoamine systems that are important in autonomic and behavioral components of the stress response (Koob et al., 2014). CRF causes its effects by stimulation of CRF1R and CRF2R receptors, and displays an 18-fold greater affinity for CRF1R than CRF2R (Vaughan et al., 1995). CRF1 and CRF2 receptors are both members of the Class B/secretin family of heptahelical receptors and are encoded by two different genes (Bale and Vale, 2004). The CRF2 gene gives rise to at least two alternatively spliced isoforms: CRF2(a), expressed in neurons, and CRF2(b), expressed in peripheral tissues and non-neuronal brain structures (Bale and Vale, 2004). CRF2(a) and CRF1 receptors share about 70% amino acid homology, with a particularly high degree of conservation in regions thought to be the primary site of G- protein coupling and signal transduction (Bale and Vale, 2004). CRF receptors show distinct cellular expression patterns and/or anatomical distribution (Bale and Vale, 2004). CRF1 receptor activation is associated with increased

stress responsiveness (Koob and Heinrichs, 1999). Both CRF and CRFR1 mRNA levels are increased by stress (Makino et al., 1995; Rabadan-Diehl et al., 1996) and by intracerebral administration of CRH itself (Mansi et al., 1996). Interestingly, CRF2 receptor activation is associated with decreases in feeding and in stress responsiveness (Pelleymounter et al., 2000).

Physiological responses to stress involve the release of CRF from the paraventricular nucleus (PVN) of the hypothalamus, followed by stimulation of adrenocorticotropic hormone (ACTH) release from the anterior pituitary. ACTH, in turn, stimulates the secretion of cortisol/corticosterone from the adrenal glands (Charmandari et al., 2005; McEwen, 1999). In addition, CRF has an extensive extrahypothalamic influence across the corticostriatal-limbic regions, and plays a critical role in modulating subjective and behavioral stress responses (Koob et al., 2014). Central catecholamines, particularly noradrenaline and dopamine, are involved in modulating brain motivational pathways (including the ventral tegmental area [VTA], nucleus accumbens [NAc], and medial prefrontal [mPFC] regions) that are important in regulating distress, exerting cognitive and behavioral control, and tempering behavioral and cognitive responses critical for adaptation and homeostasis (Paulus, 2007; Phan et al., 2005). The hypothalamic and extrahypothalamic CRF pathways and central catecholamines target brain motivational pathways to critically affect adaptive and homeostatic processes (Sinha, 2008). CRF dysregulation has been linked to the pathophysiology of mood and anxiety disorders (Nemeroff, 1996; Sinha, 2008). During stress, release of limbic CRF can modulate monoamine systems that have been implicated in mood and cognition (Valentino and Van Bockstaele, 2008; McEwen et al., 2009). Although activation of both the HPA axis and central monoaminergic systems by CRF during acute stress is adaptive, the inappropriate or persistent activation of these systems can have adverse consequences leading to psychopathology.

The clinical and preclinical data reviewed above suggest that females might be endowed with a hormonal capacity to differentially regulate stress-induced behaviors and hormonal responses (Goldstein et al., 2010). This idea is exemplified by results obtained from the Trier Social Stress Test (TSST) (Kirschbaum, 1993), an anxiogenic, social-evaluative laboratory setting that reliably activates the human HPA axis. Studies using that test have found that women secrete less salivary cortisol than men (Kudielka and Kirschbaum, 2005; Schoofs and Wolf, 2011), and report overall more irritability and distress after the test (Kelly et al., 2008). It has also been reported that estrogens can positively regulate CRF gene expression (Vamvakopoulos and Chrousos, 1993).

Gender-dependent effects of CRF

Preclinical studies have also shown that female rodents have higher basal levels of the glucocorticoid, corticosterone, than maless (Weinstock et al. 1998; Viau et al., 2005). In response to stress, female rodents release more ACTH and corticosterone than males and their stress hormone levels remain elevated for a longer period of time (Viau et al., 2005; Luine, 2008; Iwasaki-Sekino et al., 2009). Female rodents have increased CRF expression in the PVN under basal conditions, especially in the presence of high estrogen levels (Viau et al., 2005; Iwasaki-Sekino et al., 2009). In contrast, restraint stress and chronic mild stress

increase CRF mRNA in the PVN to a greater degree in males than females (Sterrenburg et al., 2012). The lack of increases in females might be due to the already high basal CRF expression in these animals (Viau et al., 2005; Sterrenburg et al., 2012). Recently, sex-specific epigenetic modifications of the CRF gene have been identified following stress, underscoring the important contribution of epigenetic factors to differences in the CRF expression (Sterrenburg et al., 2012).

It is important to note that the promoter region of the CRF gene contains both estrogen and androgen response elements, providing a partial explanation for the differential regulation of CRF gene expression (Vamvakopoulos and Chrousos, 1993; Bao et al., 2006). Indeed, gonadal steroid hormone receptors co-localize with CRF in neurons in the PVN (Bao et al., 2005, 2006). Also, estrogen stimulates CRF expression in the PVN, while androgens suppress its expression (Lund et al., 2004; Figueiredo et al., 2007). Although similar studies in humans are limited, Bao and Swaab (2007) found more hypothalamic CRF neurons in men with conditions that increased their estrogen levels above those of healthy male controls (i.e., estrogen therapy or estrogen producing tumors).

CRF has been shown to trigger various biochemical and behavioral changes in animals (Koob and Zorrilla, 2010). For example, infusion of CRF by itself into the NAC caused increased locomotor activity (Holahan et al., 1997) and also, low doses of CRF can potentiate stereotypic behaviors caused by amphetamine (Cole and Koob, 1989). The behavioral effects are most probably due to the widespread distribution of CRF and of its receptors in the mammalian brain (Perrin and Vale, 1999). Recently, it has been demonstrated that psychostimulants of diverse classes can regulate CRF mRNA levels in the brain. Binge cocaine administration can also cause increases in CRF in rat brain (Zhou et al., 1996). Acute methamphetamine administration also increases CRF expression in the NAc of male rats (Cadet et al., 2014; Martin et al., 2012). Taken together, these results support the role of CRF in the mediation of the acute effects of psychostimulants, but it remains to be determined to what extent these changes in expression are sexually dimorphic.

Oxytocin and arginine-vasopressin in neuropsychiatry

Oxytocin was first discovered by Dale (1906) who found that extracts from the human posterior pituitary gland contracted the uterus of a pregnant cat. OXY is a nine amino acid CNS neuropeptide, which was the first polypeptide hormone to be sequenced and synthesized by du Vigneaud (1956). Cells originating in the PVN have specific pathways that efficiently deliver OXY to other structures in the brain including the amygdala, bed nucleus of the stria terminalis (BNST), septum, hippocampus and NAc (Stoop, 2012). OXY 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). The neural architecture of the oxytocinergic system is evolutionarily conserved and targets brain areas critical for emotion regulation (e.g., amygdala, lateral septum, and brainstem) (Lee et al., 2009). In contrast, the regional expression of OXY receptors is highly variable and explains differences in social attachment within and between species (Young and Wang, 2004). OXY exerts anxiolytic and antidepressive effects in various models (Neumann and Landgraf, 2012).

OXY, in conjunction with DA, is essential for pair bonding in prairie voles (Aragona et al., 2006) and facilitates pup retrieval and licking in rats (Keer and Stern, 1999). Infusion of OXY into the VTA increases dopaminergic activity in the NAc (Shahrokh et al., 2010) and stimulation of oxytocinergic projections within the VTA increases extracellular DA within the NAc while concurrently inducing penile erection (Melis et al., 2007). OXY-induced dopaminergic release within the mesolimbic DA system may impact the attribution of incentive salience to a variety of social stimuli (e.g. infants, conspecifics, mates) and ultimately influence an organism's drive towards such objects (Insel, 2003; Lim and Young, 2006). Nevertheless, the modulation of motivational neural circuits by OXY does not appear to be limited to the social/reproductive realm. OXY has antinociceptive properties when introduced into the amygdala and the NAc, both terminal fields of dopaminergic VTA projections that are involved in the integration and regulation of salient information, including that associated with painful stimuli (Scott et al., 2006; Han and Yu 2009). Along similar lines, OXY has been shown to alter central dopaminergic responses associated with non-social behaviors, including addictive behaviors and stress (McGregor and Bowen, 2012). Thus, it has been hypothesized that although it may have evolved as a mechanism to promote maternal, affiliative, and sexual behaviors that are keys to reproductive success, OXY might also impact neurobiological mechanisms that subserve other functions, such as reward-seeking, drug taking, stress and pain responsiveness (Love et al., 2012).

In healthy humans, effects of OXY administration on stress reactivity include decreases in subjective stress ratings (Heinrichs et al., 2003) and decreases in salivary cortisol levels (Ditzen et al., 2009). In humans, an increase in plasma OXY was found after exposure to uncontrollable noise in women (Sanders et al., 1990) and in response to several types of psychosocial stressors (Hoge et al., 2008; Taylor et al. 2010). OXY release during stressful situations might serve to dampen physiological stress levels, because high basal plasma OXY levels are associated with low norepinephrine levels, lower blood pressure, and decreased heart rate (Light et al., 2004).

Preclinical studies have also linked OXY to stress regulation (Mc Gregor et al., 2012). Specifically, a wide variety of stressful stimuli that include conditioned fear stimuli and restraint stress cause increased central and peripheral OXY levels (Neumann et al., 2000; Onaka, 2004). In rats, OXY binding to its receptor in the amygdala inhibited activity of neural populations that project to hypothalamic and brainstem areas to regulate peripheral stress and fear responses, respectively (Huber et al., 2005; Viviani et al., 2011). Neuroimaging studies have shown that intra-nasal OXY administration decreased amygdala activity (Domes et al., 2007) and functional coupling between the amygdala and brainstem (Kirsch et al., 2005) in healthy males facing negative emotional stimuli. In addition, during rest conditions, intranasal OXY influenced amygdala functioning by increasing amygdala-prefrontal cortex (PFC) connectivity (Sripada et al., 2013). Although very few studies have been conducted in females, intranasal OXY may actually increase amygdala reactivity to negative emotional stimuli in healthy females (Domes et al., 2010). Furthermore, OXY gene polymorphism might explain inter-individual differences in dopaminergic responses to stress and in the emotional well being of women (Love et al., 2012).

Interestingly, both OXY and AVP may be particularly important for linking social signals to reinforcement pathways (Insel, 2003). These neuropeptides are released by sociosexual experience and may serve as important mediators of the activation of reward circuitries during parturition, copulation, and lactation (Insel, 2003). This line of reasoning is supported by evidence of an involvement of mesocorticolimbic pathways during mother–infant interactions in rats (Morrell et al., 2011). For example, dopamine is released (Hansen, et al., 1993) and c-fos is activated in the NAc (Lonstein et a., 1998) in maternal females following exposure to pups. This idea is further supported by the findings that VTA or NAc lesions can disrupt maternal behavior (Gaffori and Le Moal, 1979; Hansen, et al., 1991). It is also important to note that administration of low or high doses of cocaine can disrupt normal maternal behavior in rats (Morrell et al., 2011).

Of direct relevance to the issue of gender and addiction, OXY has been shown to influence the biochemical and behavioral effects of various drugs of abuse (McGregor and Bowen, 2012). Exogenously administered OXY decreased cocaine-induced hyperactivity, locomotor sensitization, and stereotyped behaviors in rodents (Sarnyai, 2011). and antagonized cocaine-induced increases in dopamine utilization in the NAc (Kovàcs et al., 1990). Conversely, cocaine administration decreased hippocampal, preoptic, and hypothalamic OXY levels (Johns et al., 1993; Elliott et al. 2001).

METH might also influence the function of CNS OXY pathways. For example, METH-induced FOS expression in the NAc core, but not shell, was significantly reduced by OXY (Carson et al., 2010b). More recently, intracerebroventricular OXY was shown to inhibit METH-induced place preference, to facilitate the extinction of METH-induced CPP, and to prevent stress-induced reinstatement of METH taking in mice (Qi et al., 2009). The effects of OXY on METH-induced behavioral activation and FOS expression might be due to OXY-mediated reduction of methamphetamine-induced dopamine efflux in the NAc (Qi et al., 2008). Additionally, OXY is known to inhibit prefrontal glutamate release during stress-induced reinstatement of METH place preference (Qi et al., 2008). It is also of interest that OXY can also block intravenous METH self-administration in rats (Carson et al., 2010a). In rats, systemic administration of OXY, or microinjections of OXY directly into the NAc,or subthalamic nucleus, can also reduce METH-induced CPP (Baracz et al., 2012). Overall, these findings suggest that addiction to various psychostimulants might trigger substantial neuroadaptations in OXY systems in the mammalian brain. The potential that there might be co-regulation of another closely related neuropeptide, AVP, also needs to be considered.

AVP was first described as a circulating neurohypophyseal antidiuretic hormone (Sawyer, 1967). Vasopressin is genetically and structurally related to OXY, and both OXY and vasopressin evolved by duplication from a common ancestral molecule, presumed to be vasotocin (Goodson et al., 2012). AVP is found predominantly in the hypothalamus but is also located in other brain regions including the NAc (Rodríguez-Borrero et al., 2010), where it interacts with specific AVP receptors (Peter et al., 1995). Vasopressin influences complex social behavior and emotional states, including, but not limited to, aggression, fear, and anxiety (Caldwell et al., 2008; Raggenbass, 2008). The social/emotional effects of vasopressin (i.e., enhanced aggression, fear, and anxiety) appear to be mediated centrally by the AVP1A receptor (Zink et al., 2010), which are present in lateral septum, hypothalamus,

bed nucleus of the stria terminalis, hippocampus, amygdala, brainstem (Loup et al., 1991; Young et al., 1999), and in monkey prefrontal cortex and cingulate cortex (Young et al., 1999). In contrast, AVP1B receptors are located on corticotropes in the anterior pituitary and, similar to corticotropin-releasing factor, stimulate the release of ACTH from the anterior pituitary (Aguilera et al. 1994). It has been suggested that AVP1B receptors coordinate the activation of the stress-responsive HPA axis by driving the processing and release of the constitutive peptides, ACTH and beta-endorphin, of pro-opiomelanocortin (POMC) (Zhou et al., 2008).

Intranasal administration of AVP has been found to modulate the activity and connectivity patterns within prefrontal cortex-amygdala regions, circuitries that are implicated in threat perception, processing of anxiety/fear, and other social behaviors (Zink et al., 2010). AVP is co-regulated with CRH (Makino et al., 1995), and AVP-expressing hypothalamic neurons co-express CRHR1 and CRHR2 receptors (Arima and Aguilera, 2000). OXY and AVP also modulate anxiety responses and fear extinction in the central amygdala of rats in opposite manners, and target distinct neuronal populations (Huber et al., 2005, Viviani et al., 2011). Following local release, OXY attenuates fear responses by acting on two major populations of neurons of an inhibitory network, one that is inhibited by OXY but excited by AVP (via AVPR1A) whereas the other is excited by OXY but unresponsive to AVP (Huber et al., 2005, Viviani et al., 2011). Interestingly, psychostimulant administration can alter AVP expression in dopaminergic areas. Specifically, cocaine can increase AVP mRNA in the NAc (Rodríguez-Borrero et al., 2010). In addition, protracted withdrawal from a chronic escalated cocaine treatment induced increases of both plasma ACTH and corticosterone levels and AVP mRNA levels in the PVN of the hypothalamus (Zhou et al. 2011). Furthermore, Cadet et al. (2014) showed recently that METH administration induced prolonged increases in AVP mRNA levels in the NAc (Cadet et al., 2014). A single injection of METH was shown to cause long-lasting alterations in CRF, OXY and AVP expression in the NAc of male rats (Cadet et al., 2014). These findings implicate significant functional interactions between OXY and AVP on drug-induced behaviors and stress-triggered reinstatement of drug-taking behaviors after long abstinence intervals.

Gender-dependent effects of OXY and AVP

The existence of sexual dimorphic responses in the OXY and AVP systems in the brain might provide a partial explanation for the higher incidence of anxiety disorders and depression in women or antisocial behavior in males (Neumann and Landgraf, 2012). Interestingly, estrogen regulates OXY expression in the magnocellular neurons of the hypothalamus and in other neuronal populations in the brain (Nomura et al., 2002). The idea that sex-dependent activity of the brain OXY system might be involved in the prevalence of some neuropsychiatric disorders is supported by sexually dimorphic reactivity of the amygdala after intranasal OXY administration (Domes et al., 2010), and by the gender-dependent impact of genetic variations in the OXY receptor upon hypothalamic and amygdala volume (Inoue et al., 2010; Tost et al., 2010). The mechanisms underlying anxiolytic and antidepressive effects of OXY are likely due to interactions with serotonergic and CRF systems, both of which have been implicated in anxiety disorders and depression (de Kloet and Holsboer,. 2005; McEwen, 2010). A subpopulation of OXY-receptor-

expressing serotonergic neurons does exist within the raphe nucleus (Yoshida et al., 2009). Moreover, stimulation of serotonin release activates hypothalamic OXY neurons in male rats (Javed et al., 1999). Furthermore, both serotonin and OXY are potential targets of estradiol in female rhesus monkeys (Michopoulos et al., 2011). Importantly, sex steroids can affect both OXY synthesis and its receptors (Gimpl and Fahrenholz, 2001). Indeed, the expression of both OXY and its receptor is modulated by estrogen in female rats (Young et al., 1997, Shughrue et al., 2002). Specifically, estrogen was shown to significantly increase the levels of OXY receptor mRNA in the ventromedial nucleus of the hypothalamus (VMH) whereas estradiol down-regulated oxytocin mRNA in the PVN of ovariectomized rats (Shughrue et al., 2002).

Although both OXY and AVP have specific functions in both males and females (Neumann and Landgraf, 2012), some of these effects appear to differ between the sexe (De Vries and Panzica, 2006; Taylor et al., 2010).

Notably, neuroanatomical studies have revealed gender differences in vasopressin neurons located in the bed nucleus of the stria terminalis (BNST) and medial amygdala (MeA), with males having more cells and denser projections than females (De Vries et al., 1981). AVP expression in these areas was also found to depend on circulating gonadal steroids (De Vries et al., 1984). These projections have been implicated in social and reproductive behaviors but also in autonomic functions (Crestani et al., 2013). Importantly, BNST and MeA AVP systems innervate regions containing major modulatory neurotransmitters including serotonin and dopamine and, thus, may be involved in regulating behavioral states (Rood et al., 2013) that are triggered by drugs of abuse and/or stressful conditions. This line of argument is consistent with several pieces of preclinical and clinical data that suggest that some effects of vasopressin on emotional states are sexually dimorphic (Bielsky et al., 2005; Thompson et al., 2006; De Vries, 2008). For example, vasopressin was elevated in men, but not in women, experiencing distress in pair-bond relationships (Taylor et al., 2010). Of related interest, AVP projections from the BST and MeA are also sensitive to circulating gonadal hormones (De Vries et al., 1984). Gonadectomy eliminates AVP expression while hormone replacement reinstates normal AVP expression (e.g. De Vries et al., 1984; Miller et al., 1992). In contrast to OXY, AVP is mainly influenced by testosterone, for the most part, via androgen receptor-mediated mechanisms (De Vries and Södersten, 2009).Of related interest, AVP is important for the modulation of aggressive behaviors in males and females (Febo and Ferris, 2014). Working in concert, affiliation and aggression are used to maintain appropriate interactions within social groups. Aggression is thought to allow for greater access to resources whereas affiliative interactions allow for reproductive and parental behaviors (Carter, 2014). The stimulatory effects of AVP on male rodent aggression have been well documented (Ferris et al., 1997; Stribley and Carter, 1999). It appears, nevertheless, that AVP might mediate rat maternal aggression through a sex-specific anxiety-mediated inhibitory mechanism (Nephew and Bridges, 2008). AVP also acts to inhibit aggression in lactating females as documented by lesion studies (Giovenardi et al., 1997). In females, endogenous AVP was reported to inhibit maternal aggression by stimulation of V1a receptors (Nephew and Bridges, 2008). Recent animal imaging studies have shown that AVP and OXY play major roles in modulating brain regions involved in regulating emotional states (Reed et al., 2013) and agonistic behaviors (Ferris et al., 2008).

Across several of these studies, it appears that both neuropeptides might modulate the functions of important neuronal networks that subsume important roles in controlling reward salience and affiliative behaviors. These networks appear to connect various nuclei within the basal forebrain, amygdala, and midbrain nuclei, as well as several cortical brain regions (Febo and Ferris, 2014).

Because both OXY and AVP are located in brain regions that are stress-sensitive, it will be of interest to investigate in greater depth the role that these two related peptides might play in some sexually dimorphic effects of psychostimulants in drug addicted populations. It will also be of interest to investigate potential treatment responses in models of stress-induced reinstatement in animal models of addiction.

Treatment implications

The preclinical and clinical data reviewed above suggest the need to develop more targeted interventions and to identify robust biomarkers for risks and resilience that are gender-specific across a range of addictions. This argument is supported by the existence of gender differences in both preclinical and clinical studies. For example, increased corticostriatal-limbic activity during craving in cocaine-dependent subjects appears to be segregated according to gender (Potenza et al., 2012). Potenza et al. (2012) have suggested that stress-reduction techniques (for women) and training to manage exposure to drug cues (for men) might be helpful in decreasing hyperresponsiveness of corticostriatal-limbic regions and restore the ability to discriminate between relevant and irrelevant stimuli.

Of interest to the discussion of the role of neuropeptides in addiction, it has been suggested that some drug users might have become “bonded” to their drugs of choice and/or to drug-related cues that are the essential ingredients of their daily activities, often, to the exclusion of other forms of reward (Robinson and Berridge, 1993, Edwards and Self, 2006). This is exemplified by the report that cocaine-using mothers have low plasma OXY levels, show increased hostility and depression, and tend to hold their infants less frequently than other mothers (Light et al., 2004). If these behaviors are related to the low OXY levels, OXY treatment might serve to ameliorate the negative effects of cocaine use on maternal behavior and improve their affiliative interactions with their children. This idea needs to be tested experimentally, while keeping in mind the context-dependency and inter-individual aspects of the effects of OXY (Olff et al., 2013). For example, when social cues in the environment are interpreted as safe or positive, OXY may promote prosocial behaviors and normal adaptive stress responses (Olff et al., 2013), but when the social cues are interpreted as unsafe or negative, OXY may promote negative perceptions of others and induce defensive and, in effect, ‘‘anti-social’’ behaviors and also less adaptive stress responses (Olff et al., 2013). This caveat suggests the need for large-scale clinical testing of OXY in addicted populations in order to clarify which specific populations can be helped by this interesting neuropeptide.

CONCLUSIONS

In summary, we have reviewed the existing literature on the effects of three neuropeptides on gender-specific prevalence of psychostimulant addiction. These hormones appear to

negatively or positively impact drug-induced behaviors and biochemical changes in the brain. In the case of CRF, the possibility exists that this peptide might play important roles during withdrawal from several illicit agents (Koob et al., 2014). It would thus be of interest to use large populations of patients to investigate to what extent CRF antagonists (Logrip et al., 2011) might differentially affect drug responses and abstinence in men and women. Of further interest is the noted bi-directionality of the interactions of OXY and AVP with other systems implicated in addiction. These include the neurotransmitters dopamine, serotonin, and CRF which might provide the tuning of responses to internal and/or external challenges (Buisman-Pijlman et al., 2014). This issue is important because OXY has been shown to inhibit CRF-mediated activation of the HPA axis and of the forebrain (Windle et al., 2004; Dabrowska et al., 2011). Chronic exposure to psychostimulants might trigger long-term epigenetic, transcriptional, and translational alterations in factors that regulate AVP, CRF, and OXY to such an extent as to alter or interfere with normal feedback mechanisms that control neuronal homeostasis. Dysfunctions in these systems might influence susceptibility to excessive drug taking in a sexually dimorphic way. This review thus suggests that more attention needs to be given to the gender distribution of patients when planning studies that might impact neuroendocrine stress and/or affiliative systems.

Acknowledgments

This paper is supported by the Intramural Research Program of the National Institute on Drug Abuse (NIDA), NIH, and DHHS (JLC). V. Bisagno is supported by grants PIP11420100100072 and PICT 2012- 0924, Argentina.

REFERENCES

Abercrombie ED, Keefe KA, DiFrischia DS, Zigmond MJ. Differential effect of stress on in vivo dopamine release in striatum, nucleus accumbens, and medial frontal cortex. J Neurochem. 1989; 52:1655–58. [PubMed: 2709017]

Aguilera G, Pham Q, Rabadan-Diehl C. Regulation of pituitary vasopressin receptors during chronic stress: relationship to corticotroph responsiveness. J Neuroendocrinol. 1994; 6:299–304. [PubMed: 7612075]

Ahmed SH, Koob GF. Cocaine- but not food-seeking behavior is reinstated by stress after extinction. Psychopharmacology (Berl). 1997; 132:289–95. [PubMed: 9292629]

Andrews JA, Tildesley E, Hops H, Li F. The influence of peers on young adult substance use. Health Psychol. 2002; 2:349–57. [PubMed: 12090677]

Anker JJ, Carroll ME. The role of progestins in the behavioral effects of cocaine and other drugs of abuse: human and animal research. Neurosci Biobehav Rev. 2010; 35:315–33. [PubMed: 20398693]

Anker JJ, Larson EB, Gliddon LA, Carroll ME. Effects of progesterone on the reinstatement of cocaine-seeking behavior in female rats. Exp Clin Psychopharmacol. 2007; 15:472–80. [PubMed: 17924781]

Antelman SM, Eichler AJ, Black CA, Kocan D. Interchangeability of stress and amphetamine in sensitization. Science. 1980; 207:329–31. [PubMed: 7188649]

Aragona BJ, Liu Y, Yu YJ, Curtis JT, Detwiler JM, et al. Nucleus accumbens dopamine differentially mediates the formation and maintenance of monogamous pair bonds. Nat Neurosci. 2006; 9:133–39. [PubMed: 16327783]

Arima H, Aguilera G. Vasopressin and oxytocin neurones of hypothalamic supraoptic and paraventricular nuclei co-express mrna for type-1 and type-2 corticotropin-releasing hormone receptors. J Neuroendocrinol. 2000; 12:833–42. [PubMed: 10971808]

Bale TL, Vale WW. Crf and crf receptors: role in stress responsivity and other behaviors. Annu Rev Pharmacol Toxicol. 2004; 44:525–57. [PubMed: 14744257]

Bangasser DA, Curtis A, Reyes BA, Bethea TT, et al. Sex differences in corticotropin-releasing factor receptor signaling and trafficking: potential role in female vulnerability to stress-related psychopathology. Mol Psychiatry. 2010; 15:896–904.

Bao A-M, Swaab DF. Gender difference in age-related number of corticotropin-releasing hormone-expressing neurons in the human hypothalamic paraventricular nucleus and the role of sex hormones. Neuroendocrinology. 2007; 85:27–36. [PubMed: 17308368]

Bao A-M, Hestiantoro A, Van Someren EJW, Swaab DF, Zhou J-N. Colocalization of corticotropin-releasing hormone and oestrogen receptor-alpha in the paraventricular nucleus of the hypothalamus in mood disorders. Brain. 2005; 128:1301–13. [PubMed: 15705605]

Bao A-M, Fischer DF, Wu Y-H, Hol EM, Balesar R, et al. A direct androgenic involvement in the expression of human corticotropin-releasing hormone. Mol. Psychiatry. 2006; 11:567–76. [PubMed: 16446741]

Baracz SJ, Rourke PI, Pardey MC, Hunt GE, McGregor IS, Cornish JL. Oxytocin directly administered into the nucleus accumbens core or subthalamic nucleus attenuates methamphetamine-induced conditioned place preference. Behav Brain Res. 2012; 228:185–93. [PubMed: 22155611]

Becker JB, Hu M. Sex differences in drug abuse. Front. Neuroendocrinol. 2008; 29:36–47. [PubMed: 17904621]

Bielsky IF, Hu SB, Young LJ. Sexual dimorphism in the vasopressin system: lack of an altered behavioral phenotype in female V1a receptor knockout mice. Behav Brain Res. 2005; 164:132–136. [PubMed: 16046007]

Brady KT, Randall CL. Gender differences in substance use disorders. Psychiatr Clin North Am. 1999; 22:241–52. [PubMed: 10385931]

Brecht M-L, O'Brien A, von Mayrhauser C, Anglin MD. Methamphetamine use behaviors and gender differences. Addict Behav. 2004; 29:89–106. [PubMed: 14667423]

Breslau N, Chilcoat HD, Kessler RC, Peterson EL, Lucia VC. Vulnerability to assaultive violence: further specification of the sex difference in post-traumatic stress disorder. Psychol Med. 1999; 29:813–21. [PubMed: 10473308]

Buisman-Pijlman F, Sumracki NM, Gordon JJ, Hull PR, Carter CS, Tops M. Individual differences underlying susceptibility to addiction: role for the endogenous oxytocin system. Pharmacol Biochem Behav. 2014; 119C:22–38. [PubMed: 24056025]

Cadet JL, Bisagno V, Milroy CM. Neuropathology of substance use disorders. Acta Neuropathol. 2014a; 127:91–107. [PubMed: 24292887]

Cadet JL, Brannock C, Ladenheim B, McCoy MT, Krasnova IN, et al. Enhanced upregulation of crh mrna expression in the nucleus accumbens of male rats after a second injection of methamphetamine given thirty days later. PLoS One. 2014b; 9:e84665. [PubMed: 24475032]

Caldwell HK, Lee HJ, Macbeth AH, Young WS 3rd. Vasopressin: behavioral roles of an “original” neuropeptide. Prog Neurobiol. 2008; 84:1–24. [PubMed: 18053631]

Caine SB, Bowen CA, Yu G, Zuzga D, Negus SS, Mello NK. Effect of gonadectomy and gonadal hormone replacement on cocaine self-administration in female and male rats. Neuropsychopharmacology. 2004; 29:929–42. [PubMed: 14735136]

Carroll ME, Lynch WJ, Roth ME, Morgan AD, Cosgrove KP. Sex and estrogen influence drug abuse. Trends Pharmacol Sci. 2004; 25:273–79. [PubMed: 15120494]

Carson DS, Cornish JL, Guastella AJ, Hunt GE, McGregor IS. Oxytocin decreases methamphetamine self-administration, methamphetamine hyperactivity, and relapse to methamphetamine-seeking behaviour in rats. Neuropharmacology. 2010a; 58:38–43. [PubMed: 19560473]

Carson DS, Hunt GE, Guastella AJ, Barber L, Cornish JL, et al. Systemically administered oxytocin decreases methamphetamine activation of the subthalamic nucleus and accumbens core and stimulates oxytocinergic neurons in the hypothalamus. Addict Biol. 2010b; 15:448–63. [PubMed: 20731630]

Carter CS. Oxytocin pathways and the evolution of human behavior. Annu Rev Psychol. 2014; 65:17–39. [PubMed: 24050183]

Charmandari E, Tsigos C, Chrousos G. Endocrinology of the stress response. Annu. Rev. Physiol. 2005; 67:259–84. [PubMed: 15709959]

Cole BJ, Koob GF. Low doses of corticotropin-releasing factor potentiate amphetamine-induced stereotyped behavior. Psychopharmacology (Berl). 1989; 99:27–33. [PubMed: 2506602]

Contoreggi C, Herning RI, Na P, Gold PW, Chrousos G, et al. Stress hormone responses to corticotropin-releasing hormone in substance abusers without severe comorbid psychiatric disease. Biol. Psychiatry. 2003; 54:873–78. [PubMed: 14573313]

Crestani CC, Alves FH, Gomes FV, Resstel LB, Correa FM, Herman JP. Mechanisms in the bed nucleus of the stria terminalis involved in control of autonomic and neuroendocrine functions: a review. Curr Neuropharmacol. 2013; 11:141–59. [PubMed: 23997750]

Cui SS, Bowen RC, Gu GB, Hannesson DK, Yu PH, Zhang X. Prevention of cannabinoid withdrawal syndrome by lithium: involvement of oxytocinergic neuronal activation. J. Neurosci. 2001; 21:9867–76. [PubMed: 11739594]

Dabrowska J, Hazra R, Ahern TH, Guo J-D, McDonald AJ, et al. Neuroanatomical evidence for reciprocal regulation of the corticotrophin-releasing factor and oxytocin systems in the hypothalamus and the bed nucleus of the stria terminalis of the rat: implications for balancing stress and affect. Psychoneuroendocrinology. 2011; 36:1312–26. [PubMed: 21481539]

Dale HH. On some physiological actions of ergot. J Physiol. 1906; 34:163–206. [PubMed: 16992821]

De Kloet ER, Joëls M, Holsboer F. Stress and the brain: from adaptation to disease. Nat Rev Neurosci. 2005; 6:463–75. [PubMed: 15891777]

De Vries GJ. Sex differences in vasopressin and oxytocin innervation of the brain. Prog Brain Res. 2008; 170:17–27. [PubMed: 18655868]

De Vries GJ, Södersten P. Sex differences in the brain: the relation between structure and function. Horm Behav. 2009; 55:589–96. [PubMed: 19446075]

De Vries GJ, Buijs RM, Swaab DF. Ontogeny of the vasopressinergic neurons of the suprachiasmatic nucleus and their extrahypothalamic projections in the rat brain--presence of a sex difference in the lateral septum. Brain Res. 1981; 218:67–78. [PubMed: 7023607]

De Vries GJ, Buijs RM, Sluiter AA. Gonadal hormone actions on the morphology of the vasopressinergic innervation of the adult rat brain. Brain Res. 1984; 298:141–145. [PubMed: 6722551]

De Vries GJ, Panzica GC. Sexual differentiation of central vasopressin and vasotocin systems in vertebrates: different mechanisms, similar endpoints. Neuroscience. 2006; 138:947–55. [PubMed: 16310321]

Der-Avakian A, Bland ST, Rozeske RR, Tamblyn JP, Hutchinson MR, et al. The effects of a single exposure to uncontrollable stress on the subsequent conditioned place preference responses to oxycodone, cocaine, and ethanol in rats. Psychopharmacology (Berl). 2007; 191:909–17. [PubMed: 17211647]

Di Chiara G, Imperato A. Drugs abused by humans preferentially increase synaptic dopamine concentrations in the mesolimbic system of freely moving rats. Proc Natl Acad Sci U S A. 1988; 85:5274–78. [PubMed: 2899326]

Di Paolo T, Falardeau P, Morissette M. Striatal D-2 dopamine agonist binding sites fluctuate during the rat estrous cycle. Life Sci. 1988; 43:665–72. [PubMed: 3412110]

Ditzen B, Schaer M, Gabriel B, Bodenmann G, Ehlert U, Heinrichs M. Intranasal oxytocin increases positive communication and reduces cortisol levels during couple conflict. Biol. Psychiatry. 2009; 65:728–31. [PubMed: 19027101]

Dluzen DE, Liu B. Gender differences in methamphetamine use and responses: a review. Gend Med. 2008; 5:24–35. [PubMed: 18420163]

Domes G, Heinrichs M, Gläscher J, Büchel C, Braus DF, Herpertz SC. Oxytocin attenuates amygdala responses to emotional faces regardless of valence. Biol Psychiatry. 2007; 62:1187–90. [PubMed: 17617382]

Domes G, Lischke A, Berger C, Grossmann A, Hauenstein K, et al. Effects of intranasal oxytocin on emotional face processing in women. Psychoneuroendocrinology. 2010; 35:83–93. [PubMed: 19632787]

Donner NC, Lowry CA. Sex differences in anxiety and emotional behavior. Pflugers Arch. 2013; 465:601–26. [PubMed: 23588380]

Du Vigneaud V. Trail of sulfur research: From insulin to oxytocin. Science. 1956; 123:967–74. [PubMed: 13324123]

Edwards S, Self DW. Monogamy: dopamine ties the knot. Nat Neurosci. 2006; 9:7–8. [PubMed: 16378085]

Elliott JC, Lubin DA, Walker CH, Johns JM. Acute cocaine alters oxytocin levels in the medial preoptic area and amygdala in lactating rat dams: implications for cocaine-induced changes in maternal behavior and maternal aggression. Neuropeptides. 2001; 35:127–34. [PubMed: 11384208]

Elman I, Karlsgodt KH, Gastfriend DR. Gender differences in cocaine craving among non-treatment-seeking individuals with cocaine dependence. Am J Drug Alcohol Abuse. 2001; 27:193–202. [PubMed: 11417935]

Erb S, Stewart J. A role for the bed nucleus of the stria terminalis, but not the amygdala, in the effects of corticotropin-releasing factor on stress-induced reinstatement of cocaine seeking. J Neurosci. 1999; 19:RC35. [PubMed: 10516337]

Erb S, Salmaso N, Rodaros D, Stewart J. A role for the CRF-containing pathway from central nucleus of the amygdala to bed nucleus of the stria terminalis in the stress-induced reinstatement of cocaine seeking in rats. Psychopharmacology (Berl). 2001; 158:360–5. [PubMed: 11797056]

Evans JL, Hahn JA, Page-Shafer K, Lum PJ, Stein ES, et al. Gender differences in sexual and injection risk behavior among active young injection drug users in san francisco (the ufo study). J Urban Health. 2003; 80:137–46. [PubMed: 12612103]

Evans SM. The role of estradiol and progesterone in modulating the subjective effects of stimulants in humans. Exp Clin Psychopharmacol. 2007; 15:418–26. [PubMed: 17924776]

Evans SM, Foltin RW. Exogenous progesterone attenuates the subjective effects of smoked cocaine in women, but not in men. Neuropsychopharmacology. 2006; 31:659–74. [PubMed: 16160708]

Evans SM, Haney M, Foltin RW. The effects of smoked cocaine during the follicular and luteal phases of the menstrual cycle in women. Psychopharmacology (Berl). 2002; 159:397–406. [PubMed: 11823892]

Febo M, Ferris CF. Oxytocin and vasopressin modulation of the neural correlates of motivation and emotion: results from functional MRI studies in awake rats. Brain Res. 2014 pii: S0006-8993(14)00072-9. doi: 10.1016/j.brainres.2014.01.019.

Fernández-Ruiz JJ, de Miguel R, Hernández ML, Ramos JA. Time-course of the effects of ovarian steroids on the activity of limbic and striatal dopaminergic neurons in female rat brain. Pharmacol Biochem Behav. 1990; 36:603–6. [PubMed: 2377660]

Ferris CF, Melloni RH Jr, Koppel G, Perry KW, Fuller RW, Delville Y. Vasopressin/serotonin interactions in the anterior hypothalamus control aggressive behavior in golden hamsters. J Neurosci. 1997; 17:4331–40. [PubMed: 9151749]

Ferris CF, Stolberg T, Kulkarni P, Murugavel M, Blanchard R, Blanchard DC, Febo M, Brevard M, Simon NG. Imaging the neural circuitry and chemical control of aggressive motivation. BMC Neurosci. 2008; 9:111. [PubMed: 19014547]

Festa ED, Quinones-Jenab V. Gonadal hormones provide the biological basis for sex differences in behavioral responses to cocaine. Horm Behav. 2004; 46:509–19. [PubMed: 15555492]

Figueiredo HF, Ulrich-Lai YM, Choi DC, Herman JP. Estrogen potentiates adrenocortical responses to stress in female rats. Am J Physiol Endocrinol Metab. 2007; 292:E1173–82. [PubMed: 17179393]

Flagel SB, Akil H, Robinson TE. Individual differences in the attribution of incentive salience to reward-related cues: Implications for addiction. Neuropharmacology 56 Suppl. 2009; 1:139–48.

Ford JD, Gelernter J, DeVoe JS, Zhang W, Weiss RD, et al. Association of psychiatric and substance use disorder comorbidity with cocaine dependence severity and treatment utilization in cocaine-dependent individuals. Drug Alcohol Depend. 2009; 99:193–203. [PubMed: 18775607]

Gaffori O, Le Moal M. Disruption of maternal behavior and appearance of cannibalism after ventral mesencephalic tegmentum lesions. Physiol Behav. 1979; 23:317–23. [PubMed: 504422]

Gallop RJ, Crits-Christoph P, Ten Have TR, Barber JP, Frank A, et al. Differential transitions between cocaine use and abstinence for men and women. J Consult Clin Psychol. 2007; 75:95–103. [PubMed: 17295568]

Gimpl G, Fahrenholz F. The oxytocin receptor system: structure, function, and regulation. Physiol Rev. 2001; 81:629–83. [PubMed: 11274341]

Giovenardi M, Padoin MJ, Cadore LP, Lucion AB. Hypothalamic paraventricular nucleus, oxytocin, and maternal aggression in rats. Ann N Y Acad Sci. 1997; 807:606–9. [PubMed: 9071411]

Goldstein JM, Jerram M, Abbs B, Whitfield-Gabrieli S, Makris N. Sex differences in stress response circuitry activation dependent on female hormonal cycle. J Neurosci. 2010; 30:431–38. [PubMed: 20071507]

Goodson JL, Kelly AM, Kingsbury MA. Evolving nonapeptide mechanisms of gregariousness and social diversity in birds. Horm Behav. 2012; 61:239–50. [PubMed: 22269661]

Griffin ML, Weiss RD, Mirin SM, Lange U. A comparison of male and female cocaine abusers. Arch Gen Psychiatry. 1989; 46:122–26. [PubMed: 2913971]

Hamamura T, Fibiger HC. Enhanced stress-induced dopamine release in the prefrontal cortex of amphetamine-sensitized rats. Eur J Pharmacol. 1993; 237:65–71. [PubMed: 8359209]

Han Y, Yu L-C. Involvement of oxytocin and its receptor in nociceptive modulation in the central nucleus of amygdala of rats. Neurosci. Lett. 2009; 454:101–4. [PubMed: 19429063]

Haney M, Maccari S, Le Moal M, Simon H, Piazza P V. Social stress increases the acquisition of cocaine self-administration in male and female rats. Brain Res. 1995; 698:46–52. [PubMed: 8581502]

Hansen S, Harthon C, Wallin E, Löfberg L, Svensson K. The effects of 6-OHDA-induced dopamine depletions in the ventral or dorsal striatum on maternal and sexual behavior in the female rat. Pharmacol Biochem Behav. 1991; 39:71–7. [PubMed: 1924515]

Hansen S, Bergvall AH, Nyiredi S. Interaction with pups enhances dopamine release in the ventral striatum of maternal rats: a microdialysis study. Pharmacol Biochem Behav. 1993; 45:673–6. [PubMed: 7687357]

Heinrichs M, Baumgartner T, Kirschbaum C, Ehlert U. Social support and oxytocin interact to suppress cortisol and subjective responses to psychosocial stress. Biol Psychiatry. 2003; 54:1389–98. [PubMed: 14675803]

Hoffmann A, Spengler D. The lasting legacy of social stress on the epigenome of the hypothalamic-pituitary-adrenal axis. Epigenomics. 2012; 4:431–44. [PubMed: 22920182]

Hoge EA, Pollack MH, Kaufman RE, Zak PJ, Simon NM. Oxytocin levels in social anxiety disorder. CNS Neurosci Ther. 2008; 14:165–70. [PubMed: 18801109]

Holahan MR, Kalin NH, Kelley AE. Microinfusion of corticotropin-releasing factor into the nucleus accumbens shell results in increased behavioral arousal and oral motor activity. Psychopharmacology (Berl). 1997; 130:189–96. [PubMed: 9106918]

Hser Y-I, Evans E, Huang Y-C. Treatment outcomes among women and men methamphetamine abusers in california. J Subst Abuse Treat. 2005; 28:77–85. [PubMed: 15723735]

Huber D, Veinante P, Stoop R. Vasopressin and oxytocin excite distinct neuronal populations in the central amygdala. Science. 2005; 308:245–48. [PubMed: 15821089]

Hudson A, Stamp JA. Ovarian hormones and propensity to drug relapse: a review. Neurosci Biobehav Rev. 2011; 35:427–36. [PubMed: 20488201]

Inoue H, Yamasue H, Tochigi M, Abe O, Liu X, et al. Association between the oxytocin receptor gene and amygdalar volume in healthy adults. Biol Psychiatry. 2010; 68:1066–72. [PubMed: 20832055]

Insel TR. Is social attachment an addictive disorder? Physiol Behav. 2003; 79:351–57. [PubMed: 12954430]

Iwasaki-Sekino A, Mano-Otagiri A, Ohata H, Yamauchi N, Shibasaki T. Gender differences in corticotropin and corticosterone secretion and corticotropin-releasing factor mrna expression in the paraventricular nucleus of the hypothalamus and the central nucleus of the amygdala in response to footshock stress or psychological. Psychoneuroendocrinology. 2009; 34:226–37. [PubMed: 18849120]

Jackson LR, Robinson TE, Becker JB. Sex differences and hormonal influences on acquisition of cocaine self-administration in rats. Neuropsychopharmacology. 2006; 31:129–38. [PubMed: 15920500]

Javed A, Kamradt MC, Van de Kar LD, Gray TS. D-fenfluramine induces serotonin-mediated fos expression in corticotropin-releasing factor and oxytocin neurons of the hypothalamus, and

serotonin-independent fos expression in enkephalin and neurotensin neurons of the amygdala. Neuroscience. 1999; 90:851–58. [PubMed: 10218785]

Johns JM, Caldwell JD, Pedersen CA. Acute cocaine treatment decreases oxytocin levels in the rat hippocampus. Neuropeptides. 1993; 24:165–69. [PubMed: 8474635]

Johnson AE, Audigier S, Rossi F, Jard S, Tribollet E, et al. Localization and characterization of vasopressin binding sites in the rat brain using an iodinated linear AVP antagonist. Brain Res. 1993; 622:9–16. [PubMed: 8242389]

Kalivas PW, Duffy P. Similar effects of daily cocaine and stress on mesocorticolimbic dopamine neurotransmission in the rat. Biol Psychiatry. 1989; 25:913–28. [PubMed: 2541803]

Karatsoreos IN, McEwen BS. Psychobiological allostasis: resistance, resilience and vulnerability. Trends Cogn Sci. 2011; 15:576–84. [PubMed: 22078931]

Keer SE, Stern JM. Dopamine receptor blockade in the nucleus accumbens inhibits maternal retrieval and licking, but enhances nursing behavior in lactating rats. Physiol. Behav. 1999; 67:659–69. [PubMed: 10604835]

Kelly MM, Tyrka AR, Anderson GM, Price LH, Carpenter LL. Sex differences in emotional and physiological responses to the trier social stress test. J Behav Ther Exp Psychiatry. 2008; 39:87–98. [PubMed: 17466262]

Kendler KS, Thornton LM, Gardner CO. Stressful life events and previous episodes in the etiology of major depression in women: an evaluation of the “kindling” hypothesis. Am. J Psychiatry. 2000; 157:1243–51. [PubMed: 10910786]

Kendler KS, Ohlsson H, Sundquist K, Sundquist J. Peer Deviance, Parental Divorce, and Genetic Risk in the Prediction of Drug Abuse in a Nationwide Swedish Sample Evidence of Environment-Environment and Gene-Environment Interaction. JAMA Psychiatry. 2014 doi:10.1001/jamapsychiatry.2013.4166.

Kessler RC, Demler O, Frank RG, Olfson M, et al. Prevalence and treatment of mental disorders, 1990 to 2003. N Engl J Med. 2005; 352:2515–23. [PubMed: 15958807]

Kirsch P, Esslinger C, Chen Q, Mier D, Lis S, et al. Oxytocin modulates neural circuitry for social cognition and fear in humans. J Neurosci. 2005; 25:11489–93. [PubMed: 16339042]

Kirschbaum C, Pirke KM, Hellhammer DH. The ‘Trier Social Stress Test’--a tool for investigating psychobiological stress responses in a laboratory setting. Neuropsychobiology. 1993; 28:76–81. [PubMed: 8255414]

Koob GF, Heinrichs SC. A role for corticotropin releasing factor and urocortin in behavioral responses to stressors. Brain Res. 1999; 848:141–52. [PubMed: 10612706]

Koob G, Kreek MJ. Stress, dysregulation of drug reward pathways, and the transition to drug dependence. Am J Psychiatry. 2007; 164:1149–59. [PubMed: 17671276]

Koob GF, Zorrilla EP. Neurobiological mechanisms of addiction: focus on corticotropin-releasing factor. Curr Opin Investig Drugs. 2010; 11:63–71.

Koob GF, Buck CL, Cohen A, Edwards S, Park PE, et al. Addiction as a stress surfeit disorder. Neuropharmacology. 2014; 76(Pt B):370–82. [PubMed: 23747571]

Kosten TA, Gawin FH, Kosten TR, Rounsaville BJ. Gender differences in cocaine use and treatment response. J Subst Abuse Treat. 1993; 10:63–66. [PubMed: 8450576]

Kovàcs GL, Sarnyai Z, Barbarczi E, Szabó G, Telegdy G. The role of oxytocin-dopamine interactions in cocaine-induced locomotor hyperactivity. Neuropharmacology. 1990; 29:365–68. [PubMed: 2160623]

Kovács GL, Sarnyai Z, Szabó G. Oxytocin and addiction: a review. Psychoneuroendocrinology. 1998; 23:945–62. [PubMed: 9924746]

Kreibich AS, Blendy JA. Camp response element-binding protein is required for stress but not cocaine-induced reinstatement. J Neurosci. 2004; 24:6686–92. [PubMed: 15282271]

Kudielka BM, Kirschbaum C. Sex differences in hpa axis responses to stress: a review. Biol. Psychol. 2005; 69:113–32. [PubMed: 15740829]

Kufahl PR, Li Z, Risinger RC, Rainey CJ, Wu G, et al. Neural responses to acute cocaine administration in the human brain detected by fmri. Neuroimage. 2005; 28:904–14. [PubMed: 16061398]

Kuhn C, Johnson M, Thomae A, Luo B, Simon SA, et al. The emergence of gonadal hormone influences on dopaminergic function during puberty. Horm Behav. 2010; 58:122–37. [PubMed: 19900453]

Larson EB, Anker JJ, Gliddon LA, Fons KS, Carroll ME. Effects of estrogen and progesterone on the escalation of cocaine self-administration in female rats during extended access. Exp Clin Psychopharmacol. 2007; 15:461–71. [PubMed: 17924780]

Lee H-J, Macbeth AH, Pagani JH, Young WS. Oxytocin: the great facilitator of life. Prog Neurobiol. 2009; 88:127–51. [PubMed: 19482229]

Lee Y, Hamamura T, Ohashi K, Fujiwara Y, Kuroda S. The effect of lithium on methamphetamine-induced regional fos protein expression in the rat brain. Neuroreport. 1999; 10:895–900. [PubMed: 10321456]

Lex BW. Some gender differences in alcohol and polysubstance users. Health Psychol. 1991; 10:121–32. [PubMed: 2055210]

Leyton M, Stewart J. Preexposure to foot-shock sensitizes the locomotor response to subsequent systemic morphine and intra-nucleus accumbens amphetamine. Pharmacol Biochem Behav. 1990; 37:303–10. [PubMed: 2080193]

Lévesque D, Gagnon S, Di Paolo T. Striatal D1 dopamine receptor density fluctuates during the rat estrous cycle. Neurosci Lett. 1989; 98:345–50. [PubMed: 2524681]

Light KC, Grewen KM, Amico JA, Boccia M, Brownley KA, Johns JM. Deficits in plasma oxytocin responses and increased negative affect, stress, and blood pressure in mothers with cocaine exposure during pregnancy. Addict Behav. 2004; 29:1541–64. [PubMed: 15451123]

Lim MM, Young LJ. Neuropeptidergic regulation of affiliative behavior and social bonding in animals. Horm Behav. 2006; 50:506–17. [PubMed: 16890230]

Logrip ML, Koob GF, Zorrilla EP. Role of corticotropin-releasing factor in drug addiction: potential for pharmacological intervention. CNS Drugs. 2011; 25:271–87. [PubMed: 21425881]

Loup F, Tribollet E, Dubois-Dauphin M, Dreifuss JJ. Localization of high-affinity binding sites for oxytocin and vasopressin in the human brain. An autoradiographic study. Brain Res. 1991; 555:220–232. [PubMed: 1657300]

Love TM, Enoch M-A, Hodgkinson CA, Peciña M, Mickey B, et al. Oxytocin gene polymorphisms influence human dopaminergic function in a sex-dependent manner. Biol. Psychiatry. 2012; 72:198–206. [PubMed: 22418012]

Luine VN. Sex steroids and cognitive function. J Neuroendocrinol. 2008; 20:866–72. [PubMed: 18513207]

Lund TD, Munson DJ, Haldy ME, Handa RJ. Androgen inhibits, while oestrogen enhances, restraint-induced activation of neuropeptide neurones in the paraventricular nucleus of the hypothalamus. J Neuroendocrinol. 2004; 16:272–78. [PubMed: 15049858]

Lynch WJ. Sex differences in vulnerability to drug self-administration. Exp. Clin. Psychopharmacol. 2006; 14:34–41. [PubMed: 16503703]

Lynch WJ, Roth ME, Carroll ME. Biological basis of sex differences in drug abuse: preclinical and clinical studies. Psychopharmacology (Berl). 2002; 164:121–37. [PubMed: 12404074]

Lonstein JS, Simmons DA, Swann JM, Stern JM. Forebrain expression of c-fos due to active maternal behaviour in lactating rats. Neuroscience. 1998; 82:267–81. [PubMed: 9483519]

MacLennan AJ, Maier SF. Coping and the stress-induced potentiation of stimulant stereotypy in the rat. Science. 1983; 219:1091–93. [PubMed: 6681679]

Makino S, Smith MA, Gold PW. Increased expression of corticotropin-releasing hormone and vasopressin messenger ribonucleic acid (mrna) in the hypothalamic paraventricular nucleus during repeated stress: association with reduction in glucocorticoid receptor mrna levels. Endocrinology. 1995; 136:3299–3309. [PubMed: 7628364]

Mansi JA, Rivest S, Drolet G. Regulation of corticotropin-releasing factor type 1 (crf1) receptor messenger ribonucleic acid in the paraventricular nucleus of rat hypothalamus by exogenous crf. Endocrinology. 1996; 137:4619–29. [PubMed: 8895325]

Martin TA, Jayanthi S, McCoy MT, Brannock C, Ladenheim B, et al. Methamphetamine causes differential alterations in gene expression and patterns of histone acetylation/hypoacetylation in the rat nucleus accumbens. PLoS One. 2012; 7:e34236. [PubMed: 22470541]

McEwen BS. Stress and hippocampal plasticity. Annu Rev Neurosc. 1999; 22:105–22.

McEwen BS. Stress, sex, and neural adaptation to a changing environment: mechanisms of neuronal remodeling. Ann N Y Acad Sci 1204 Suppl:E38–59. 2010

McFall ME, Mackay PW, Donovan DM. Combat-related posttraumatic stress disorder and severity of substance abuse in vietnam veterans. J Stud Alcohol. 1992; 53:357–63. [PubMed: 1619930]

McGregor IS, Bowen MT. Breaking the loop: oxytocin as a potential treatment for drug addiction. Horm Behav. 2012; 61:331–39. [PubMed: 22198308]

McLaughlin JP, Land BB, Li S, Pintar JE, Chavkin C. Prior activation of kappa opioid receptors by u50,488 mimics repeated forced swim stress to potentiate cocaine place preference conditioning. Neuropsychopharmacology. 2006; 31:787–94. [PubMed: 16123754]

McLean CP, Anderson ER. Brave men and timid women? a review of the gender differences in fear and anxiety. Clin Psychol Rev. 2009; 29:496–505. [PubMed: 19541399]

Melis MR, Melis T, Cocco C, Succu S, Sanna F, et al. Oxytocin injected into the ventral tegmental area induces penile erection and increases extracellular dopamine in the nucleus accumbens and paraventricular nucleus of the hypothalamus of male rats. Eur J Neurosci. 2007; 26:1026–35. [PubMed: 17672853]

Michopoulos V, Checchi M, Sharpe D, Wilson ME. Estradiol effects on behavior and serum oxytocin are modified by social status and polymorphisms in the serotonin transporter gene in female rhesus monkeys. Horm Behav. 2011; 59:528–35. [PubMed: 21316367]

Miller MA, Devries GJ, al-Shamma HA, Dorsa DM. Decline of vasopressin immunoreactivity and mRNA levels in the bed nucleus of the stria terminalis following castration. J Neurosci. 1992; 12:2881–2887. [PubMed: 1494938]

Morrell JI, Basso JC, Pereira M. Both high and low doses of cocaine derail normal maternal caregiving - lessons from the laboratory rat. Front Psychiatry. 2011; 2:30. [PubMed: 21687771]

Munro CA, McCaul ME, Wong DF, Oswald LM, Zhou Y, et al. Sex differences in striatal dopamine release in healthy adults. Biol Psychiatry. 2006; 59:966–74. [PubMed: 16616726]

Nemeroff CB. The corticotropin-releasing factor (crf) hypothesis of depression: new findings and new directions. Mol. Psychiatry. 1996; 1:336–42. [PubMed: 9118360]

Nephew BC, Bridges RS. Central actions of arginine vasopressin and a V1a receptor antagonist on maternal aggression, maternal behavior, and grooming in lactating rats. Pharmacol Biochem Behav. 2008; 91:77–83. [PubMed: 18640147]

Neumann ID, Landgraf R. Balance of brain oxytocin and vasopressin: implications for anxiety, depression, and social behaviors. Trends Neurosci. 2012; 35:649–59. [PubMed: 22974560]

Neumann ID, Krömer SA, Toschi N, Ebner K. Brain oxytocin inhibits the (re)activity of the hypothalamo-pituitary-adrenal axis in male rats: involvement of hypothalamic and limbic brain regions. Regul Pept. 2000; 96:31–38. [PubMed: 11102649]

Nomura M, McKenna E, Korach KS, Pfaff DW, Ogawa S. Estrogen receptor-β regulates transcript levels for oxytocin and arginine vasopressin in the hypothalamic paraventricular nucleus of male mice. Brain Res Mol Brain Res. 2002; 109:84–94. [PubMed: 12531518]

Olff M, Frijling JL, Kubzansky LD, Bradley B, Ellenbogen MA, Cardoso C, Bartz JA, Yee JR, van Zuiden M. The role of oxytocin in social bonding, stress regulation and mental health: an update on the moderating effects of context and interindividual differences. Psychoneuroendocrinology. 2013; 38:1883–94. [PubMed: 23856187]

Onaka T. Neural pathways controlling central and peripheral oxytocin release during stress. J. Neuroendocrinol. 2004; 16:308–12. [PubMed: 15089967]

Opacka-Juffry J, Mohiyeddini C. Experience of stress in childhood negatively correlates with plasma oxytocin concentration in adult men. Stress. 2012; 15:1–10. [PubMed: 21682649]

Ouimette P, Coolhart D, Funderburk JS, Wade M, Brown PJ. Precipitants of first substance use in recently abstinent substance use disorder patients with ptsd. Addict Behav. 2007; 32:1719–27. [PubMed: 17188816]

Pacchioni AM, Gioino G, Assis A, Cancela LM. A single exposure to restraint stress induces behavioral and neurochemical sensitization to stimulating effects of amphetamine: involvement of nmda receptors. Ann N Y Acad Sci. 2002; 965:233–46. [PubMed: 12105099]

Parker G, Brotchie H. Gender differences in depression. Int Rev Psychiatry. 2010; 22:429–36. [PubMed: 21047157]

Paulus MP. Decision-making dysfunctions in psychiatry--altered homeostatic processing? Science. 2007; 318:602–6. [PubMed: 17962553]

Pelleymounter MA, Joppa M, Carmouche M, Cullen MJ, Brown B, et al. Role of corticotropin-releasing factor (crf) receptors in the anorexic syndrome induced by crf. J. Pharmacol Exp Ther. 2000; 293:799–806. [PubMed: 10869378]

Perrin MH, Vale WW. Corticotropin releasing factor receptors and their ligand family. Ann N Y Acad Sci. 1999; 885:312–28. [PubMed: 10816663]

Peter J, Burbach H, Adan RA, Lolait SJ, van Leeuwen FW, et al. Molecular neurobiology and pharmacology of the vasopressin/oxytocin receptor family. Cell Mol Neurobiol. 1995; 15:573–95. [PubMed: 8719042]

Phan KL, Fitzgerald DA, Nathan PJ, Moore GJ, Uhde TW, Tancer ME. Neural substrates for voluntary suppression of negative affect: a functional magnetic resonance imaging study. Biol Psychiatry. 2005; 57:210–19. [PubMed: 15691521]

Piazza P V, Deminière JM, Le Moal M, Simon H. Factors that predict individual vulnerability to amphetamine self-administration. Science. 1989; 245:1511–13. [PubMed: 2781295]

Piazza PV, Deroche-Gamonet V. A multistep general theory of transition to addiction. Psychopharmacology (Berl). 2013; 229:387–413. [PubMed: 23963530]

Pigott TA. Anxiety disorders in women. Psychiatr Clin North Am. 2003; 26:621–72. [PubMed: 14563101]

Post RM, Kalivas P. Bipolar disorder and substance misuse: pathological and therapeutic implications of their comorbidity and cross-sensitisation. Br J Psychiatry. 2013; 202:172–6. [PubMed: 23457180]

Potenza MN, Hong KI, Lacadie CM, Fulbright RK, Tuit KL, Sinha R. Neural correlates of stress-induced and cue-induced drug craving: influences of sex and cocaine dependence. Am J Psychiatry. 2012; 169:406–14. [PubMed: 22294257]

Qi J, Yang J-Y, Song M, Li Y, Wang F, Wu C-F. Inhibition by oxytocin of methamphetamine-induced hyperactivity related to dopamine turnover in the mesolimbic region in mice. Naunyn Schmiedebergs Arch Pharmacol. 2008; 376:441–48. [PubMed: 18092152]

Qi J, Yang J-Y, Wang F, Zhao Y-N, Song M, Wu C-F. Effects of oxytocin on methamphetamine-induced conditioned place preference and the possible role of glutamatergic neurotransmission in the medial prefrontal cortex of mice in reinstatement. Neuropharmacology. 2009; 56:856–65. [PubMed: 19371575]

Quinones-Jenab V. Why are women from venus and men from mars when they abuse cocaine? Brain Res. 2006; 1126:200–203. [PubMed: 17010952]

Rabadan-Diehl C, Kiss A, Camacho C, Aguilera G. Regulation of messenger ribonucleic acid for corticotropin releasing hormone receptor in the pituitary during stress. Endocrinology. 1996; 137:3808–14. [PubMed: 8756551]

Reed MD, Price KE, Archbold J, Moffa A, Febo M. Predator odor-evoked BOLD activation in the awake rat: modulation by oxytocin and V_1a vasopressin receptor antagonists. Brain Res. 2013; 1494:70–83. [PubMed: 23219972]

Reichel CM, Chan CH, Ghee SM, See RE. Sex differences in escalation of methamphetamine self-administration: cognitive and motivational consequences in rats. Psychopharmacology (Berl). 2012; 223:371–80. [PubMed: 22592902]

Robbins SJ, Ehrman RN, Childress AR, O'Brien CP. Comparing levels of cocaine cue reactivity in male and female outpatients. Drug Alcohol Depend. 1999; 53:223–30. [PubMed: 10080048]

Robinson TE, Berridge KC. The neural basis of drug craving: an incentive-sensitization theory of addiction. Brain Res Brain Res Rev. 1993; 18:247–91. [PubMed: 8401595]

Rodríguez-Borrero E, Rivera-Escalera F, Candelas F, Montalvo J, Muñoz-Miranda WJ, et al. Arginine vasopressin gene expression changes within the nucleus accumbens during environment elicited cocaine-conditioned response in rats. Neuropharmacology. 2010; 58:88–101. [PubMed: 19596360]

Roth ME, Carroll ME. Sex differences in the acquisition of iv methamphetamine self-administration and subsequent maintenance under a progressive ratio schedule in rats. Psychopharmacology (Berl). 2004; 172:443–49. [PubMed: 14654996]

Rood BD, Stott RT, You S, Smith CJ, Woodbury ME, De Vries GJ. Site of origin of and sex differences in the vasopressin innervation of the mouse (Mus musculus) brain. J Comp Neurol. 2013; 521:2321–58. [PubMed: 23239101]

Russo SJ, Festa ED, Fabian SJ, Gazi FM, Kraish M, et al. Gonadal hormones differentially modulate cocaine-induced conditioned place preference in male and female rats. Neuroscience. 2003; 120:523–33. [PubMed: 12890521]

Saal D, Dong Y, Bonci A, Malenka RC. Drugs of abuse and stress trigger a common synaptic adaptation in dopamine neurons. Neuron. 2003; 37:577–82. [PubMed: 12597856]

Sanchez CJ, Bailie TM, Wu W-R, Li N, Sorg BA. Manipulation of dopamine d1-like receptor activation in the rat medial prefrontal cortex alters stress- and cocaine-induced reinstatement of conditioned place preference behavior. Neuroscience. 2003; 119:497–505. [PubMed: 12770563]

Sanders G, Freilicher J, Lightman SL. Psychological stress of exposure to uncontrollable noise increases plasma oxytocin in high emotionality women. Psychoneuroendocrinology. 1990; 15:47–58. [PubMed: 2367615]

Sapolsky RM. Glucocorticoids and hippocampal atrophy in neuropsychiatric disorders. Arch Gen Psychiatry. 2000; 57:925–35. [PubMed: 11015810]

Sarnyai Z. Oxytocin as a potential mediator and modulator of drug addiction. Addict Biol. 2011; 16:199–201. [PubMed: 21371175]

Sawyer WH. Evolution of antidiuretic hormones and their functions. Am J Med. 1967; 42:678–86. [PubMed: 5337372]

Schindler CW, Bross JG, Thorndike EB. Gender differences in the behavioral effects of methamphetamine. Eur J Pharmacol. 2002; 442:231–35. [PubMed: 12065076]

Schoofs D, Wolf OT. Are salivary gonadal steroid concentrations influenced by acute psychosocial stress? a study using the trier social stress test (tsst). Int J Psychophysiol. 2011; 80:36–43. [PubMed: 21256897]

Scott DJ, Heitzeg MM, Koeppe RA, Stohler CS, Zubieta J-K. Variations in the human pain stress experience mediated by ventral and dorsal basal ganglia dopamine activity. J Neurosci. 2006; 26:10789–95. [PubMed: 17050717]

Shaham Y, Rajabi H, Stewart J. Relapse to heroin-seeking in rats under opioid maintenance: the effects of stress, heroin priming, and withdrawal. J Neurosci. 1996; 16:1957–63. [PubMed: 8774462]

Shahrokh DK, Zhang T-Y, Diorio J, Gratton A, Meaney MJ. Oxytocin-dopamine interactions mediate variations in maternal behavior in the rat. Endocrinology. 2010; 151:2276–86. [PubMed: 20228171]

Shughrue PJ, Dellovade TL, Merchenthaler I. Estrogen modulates oxytocin gene expression in regions of the rat supraoptic and paraventricular nuclei that contain estrogen receptor-beta. Prog Brain Res. 2002; 139:15–29. [PubMed: 12436923]

Sinha R. Chronic stress, drug use, and vulnerability to addiction. Ann N Y Acad Sci. 2008; 1141:105–30. [PubMed: 18991954]

Sinha R, Jastreboff AM. Stress as a common risk factor for obesity and addiction. Biol Psychiatry. 2013; 73:827–35. [PubMed: 23541000]

Sinha R, Li CSR. Imaging stress- and cue-induced drug and alcohol craving: association with relapse and clinical implications. Drug Alcohol Rev. 2007; 26:25–31. [PubMed: 17364833]

Sofuoglu M, Dudish-Poulsen S, Nelson D, Pentel PR, Hatsukami DK. Sex and menstrual cycle differences in the subjective effects from smoked cocaine in humans. Exp Clin Psychopharmacol. 1999; 7:274–83. [PubMed: 10472516]

Sofuoglu M, Mitchell E, Kosten TR. Effects of progesterone treatment on cocaine responses in male and female cocaine users. Pharmacol Biochem Behav. 2004; 78:699–705. [PubMed: 15301924]

Sorg BA, Kalivas PW. Effects of cocaine and footshock stress on extracellular dopamine levels in the medial prefrontal cortex. Neuroscience. 1993; 53:695–703. [PubMed: 7683777]

Sripada CS, Phan KL, Labuschagne I, Welsh R, Nathan PJ, Wood AG. Oxytocin enhances resting-state connectivity between amygdala and medial frontal cortex. Int. J. Neuropsychopharmacol. 2013; 16:255–60. [PubMed: 22647521]

Sterrenburg L, Gaszner B, Boerrigter J, Santbergen L, Bramini M, et al. Sex-dependent and differential responses to acute restraint stress of corticotropin-releasing factor-producing neurons in the rat paraventricular nucleus, central amygdala, and bed nucleus of the stria terminalis. J Neurosci Res. 2012; 90:179–92. [PubMed: 21922520]

Stoop R. Neuromodulation by oxytocin and vasopressin. Neuron. 2012; 76:142–59. [PubMed: 23040812]

Stribley JM, Carter CS. Developmental exposure to vasopressin increases aggression in adult prairie voles. Proc Natl Acad Sci U S A. 1999; 96:12601–4. [PubMed: 10535968]

Taylor SE, Saphire-Bernstein S, Seeman TE. Are plasma oxytocin in women and plasma vasopressin in men biomarkers of distressed pair-bond relationships? Psychol Sci. 2010; 21:3–7. [PubMed: 20424014]

Tetrault JM, Desai RA, Becker WC, Fiellin DA, Concato J, Sullivan LE. Gender and non-medical use of prescription opioids: results from a national us survey. Addiction. 2008; 103:258–68. [PubMed: 18042194]

Thompson RR, George K, Walton JC, Orr SP, Benson J. Sex-specific influences of vasopressin on human social communication. Proc Natl Acad Sci U S A. 2006; 103:7889–7894. [PubMed: 16682649]

Tolin DF, Foa EB. Sex differences in trauma and posttraumatic stress disorder: a quantitative review of 25 years of research. Psychol Bull. 2006; 132:959–92. [PubMed: 17073529]

Tost H, Kolachana B, Hakimi S, Lemaitre H, Verchinski BA, et al. A common allele in the oxytocin receptor gene (oxtr) impacts prosocial temperament and human hypothalamic-limbic structure and function. Proc Natl Acad Sci U S A. 2010; 107:13936–41. [PubMed: 20647384]

Triffleman EG, Marmar CR, Delucchi KL, Ronfeldt H. Childhood trauma and posttraumatic stress disorder in substance abuse inpatients. J Nerv Ment Dis. 1995; 183:172–76. [PubMed: 7891064]

Vale W, Spiess J, Rivier C, Rivier J. Characterization of a 41-residue ovine hypothalamic peptide that stimulates secretion of corticotropin and beta-endorphin. Science. 1981; 213:1394–1397. [PubMed: 6267699]

Valentino RJ, Van Bockstaele E. Convergent regulation of locus coeruleus activity as an adaptive response to stress. Eur J Pharmacol. 2008; 583:194–203. [PubMed: 18255055]

Vamvakopoulos NC, Chrousos GP. Evidence of direct estrogenic regulation of human corticotropin-releasing hormone gene expression. potential implications for the sexual dimophism of the stress response and immune/inflammatory reaction. J Clin Invest. 1993; 92:1896–1902. [PubMed: 8408641]

Vaughan J, Donaldson C, Bittencourt J, Perrin MH, Lewis K, et al. Urocortin, a mammalian neuropeptide related to fish urotensin i and to corticotropin-releasing factor. Nature. 1995; 378:287–92. [PubMed: 7477349]

Viau V, Bingham B, Davis J, Lee P, Wong M. Gender and puberty interact on the stress-induced activation of parvocellular neurosecretory neurons and corticotropin-releasing hormone messenger ribonucleic acid expression in the rat. Endocrinology. 2005; 146:137–46. [PubMed: 15375029]

Viviani D, Charlet A, van den Burg E, Robinet C, Hurni N, et al. Oxytocin selectively gates fear responses through distinct outputs from the central amygdala. Science. 2011; 333:104–7. [PubMed: 21719680]

Volkow N, Li T-K. The neuroscience of addiction. Nat Neurosci. 2005; 8:1429–30. [PubMed: 16251981]

Volkow ND, Wang G-J, Fowler JS, Tomasi D, Telang F. Addiction: beyond dopamine reward circuitry. Proc Natl Acad Sci U S A. 2011; 108:15037–42. [PubMed: 21402948]

Volkow ND, Wang G-J, Fowler JS, Tomasi D. Addiction circuitry in the human brain. Annu Rev Pharmacol Toxicol. 2012; 52:321–36. [PubMed: 21961707]

Weinstock M, Razin M, Schorer-Apelbaum D, Men D, McCarty R. Gender differences in sympathoadrenal activity in rats at rest and in response to footshock stress. Int J Dev Neurosci. 1998; 16:289–95. [PubMed: 9785125]

Weiser MJ, Foradori CD, Handa RJ. Estrogen receptor beta in the brain: from form to function. Brain Res Rev. 2008; 57:309–320. [PubMed: 17662459]

Weissman MM, Bland R, Joyce PR, Newman S, Wells JE, Wittchen HU. Sex differences in rates of depression: cross-national perspectives. J Affect Disord. 1993; 29:77–84. [PubMed: 8300980]

White TL, Justice AJ, de Wit H. Differential subjective effects of D-amphetamine by gender, hormone levels and menstrual cycle phase. Pharmacol Biochem Behav. 2002; 73:729–41. [PubMed: 12213517]

Wilson N, Cadet JL. Comorbid mood, psychosis, and marijuana abuse disorders: a theoretical review. J Addict Dis. 2009; 28:309–19. [PubMed: 20155601]

Windle RJ, Kershaw YM, Shanks N, Wood SA, Lightman SL, Ingram CD. Oxytocin attenuates stress-induced c-fos mrna expression in specific forebrain regions associated with modulation of hypothalamo-pituitary-adrenal activity. J Neurosci. 2004; 24:2974–82. [PubMed: 15044536]

Yoshida M, Takayanagi Y, Inoue K, Kimura T, Young LJ, et al. Evidence that oxytocin exerts anxiolytic effects via oxytocin receptor expressed in serotonergic neurons in mice. J Neurosci. 2009; 29:2259–71. [PubMed: 19228979]

Young LJ, Wang Z. The neurobiology of pair bonding. Nat Neurosci. 2004; 7:1048–54. [PubMed: 15452576]

Young LJ, Muns S, Wang Z, Insel TR. Changes in oxytocin receptor mrna in rat brain during pregnancy and the effects of estrogen and interleukin-6. J Neuroendocrinol. 1997; 9:859–65. [PubMed: 9419837]

Young LJ, Toloczko D, Insel TR. Localization of vasopressin (V1a) receptor binding and mRNA in the rhesus monkey brain. J Neuroendocrinol. 1999; 11:291–297. [PubMed: 10223283]

Zhou Y, Litvin Y, Piras AP, Pfaff DW, Kreek MJ. Persistent increase in hypothalamic arginine vasopressin gene expression during protracted withdrawal from chronic escalating-dose cocaine in rodents. Neuropsychopharmacology. 2011; 36:2062–75. [PubMed: 21677651]

Zhou Y, Spangler R, LaForge KS, Maggos CE, Ho A, Kreek MJ. Corticotropin-releasing factor and type 1 corticotropin-releasing factor receptor messenger rnas in rat brain and pituitary during “binge”-pattern cocaine administration and chronic withdrawal. J Pharmacol Exp Ther. 1996; 279:351–58. [PubMed: 8859013]

Zhou Y, Leri F, Cummins E, Hoeschele M, Kreek MJ. Involvement of arginine vasopressin and V1b receptor in heroin withdrawal and heroin seeking precipitated by stress and by heroin. Neuropsychopharmacology. 2008; 33:226–236. [PubMed: 17443128]

Zilberman M, Tavares H, el-Guebaly N. Gender similarities and differences: the prevalence and course of alcohol- and other substance-related disorders. J Addict Dis. 2003; 22:61–74. [PubMed: 14723478]

Zink CF, Stein JL, Kempf L, Hakimi S, Meyer-Lindenberg A. Vasopressin modulates medial prefrontal cortex-amygdala circuitry during emotion processing in humans. J Neurosci. 2010; 30:7017–22. [PubMed: 20484643]