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

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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 neurocircuits 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.
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 discuss 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 US National 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 recent 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 41 amino 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 (Pellemounter 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 males (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 al., 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 (Kovács 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 (Rodriguez-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 (Agulera 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 AVP(R1A) 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 sexes (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.

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