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Review

Sex differences in the neurobiology of drug addiction

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ABSTRACT

Epidemiological data demonstrate that while women report lower rates of drug use than men, the number of current drug users and abusers who are women continues to increase. In addition women progress through the phases of addiction differently than men; women transition from casual drug use to addiction faster, are more reactive to stimuli that trigger relapse, and have higher rates of relapse then men. Sex differences in physiological and psychological responses to drugs of abuse are well documented and it is well established that estrogen effects on dopamine (DA) systems are largely responsible for these sex differences. However, the downstream mechanisms that result from interactions between estrogen and the effects of drugs of abuse on the DA system are just beginning to be explored. Here we review the basic neurocircuitry which underlies reward and addiction; highlighting the neuroadaptive changes that occur in the mesolimbic dopamine reward and anti-reward/stress pathways. We propose that sex differences in addiction are due to sex differences in the neural systems which mediate positive and negative reinforcement and that these differences are modulated by ovarian hormones. This forms a neurobehavioral basis for the search for the molecular and cellular underpinnings that uniquely guide motivational behaviors and make women more vulnerable to developing and sustaining addiction than men.

Contents

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Introduction

Addiction is a chronic, potentially relapsing, neurological illness characterized by a loss of control over drug seeking and intake. Addictive substances include illicit drugs like cocaine and heroin, as well as legally available nicotine and alcohol. Moreover, prescription drugs, such as opioids, stimulants, and depressants are also increasingly being used for non-medical reasons (Compton and Volkow, 2006). Chronic repeated use of these drugs hijacks normal motivated behaviors via the dysregulation of brain reward circuitry (Hyman et al., 2006). While contributions of the neural substrates underlying addiction are being characterized with increasing precision, the overwhelming majority of investigations into brain reward and anti-reward circuitry has been – and continues to be – conducted in men and/or male animals. Until the early 1990s research on the etiology and treatment of addiction was conducted on a male only population because prior to this time the notion that men and women differed only in their reproductive abilities and secondary sex characteristics was embedded in clinical research. Over the past few decades, awareness of the importance of sex differences in addiction has grown and, as a result, an emergent field devoted to characterizing sex differences has and continues to develop (Evans, 2007).

Prevalence

Results of the 2012 National Survey on Drug Use and Health (NSDUH), estimated 9.2% (23.9 million) of Americans, age 12 or older were current (had used in the past 30 days) illicit drug users. While women exhibit lower rates of drug use and addiction than men, prevalence rates indicate that the number of female drug abusers has increased and continues to escalate (SAMHSA, 2012). Evidence identifying important differences in the pattern of drug use and abuse between men and women suggests that gender also influences the course and treatment of substance use disorder. In general, women progress from casual drug use to dependence more rapidly, experience higher levels of craving and relapse during periods of abstinence, take larger amounts of the substance during bouts of relapse, and are less likely to seek treatment for their addiction than men (Brady and Randall, 1999; Ignjatova and Raleva, 2009; Kosten et al., 1985) In addition, women who enter drug abuse treatment programs have a more severe addiction syndrome and higher prevalence of co-occurring mental health disorders (Back et al., 2011; Yates et al., 1993).

Sex differences and influence of ovarian hormone on addiction behaviors

Human studies

The acute subjective effects of most drugs of abuse, except stimulants (cocaine and amphetamine), do not differ between men and women (Terner and de Wit, 2006). In the case of psychostimulants, men often report (but, not reliably) greater subjective effects than women (Lukas et al., 1996). This lack of reliability is likely due to the fact that women's reporting of the subjective effects of their response to psychostimulants varies with the menstrual cycle (Fig. 1). Women have greater subjective responses to cocaine in the follicular phase of the menstrual cycle, when levels of estrogen are rising and progesterone levels are minimal (Evans and Foltin, 2006a; Evans et al., 2002; Sofuoglu et al., 1999). In the luteal phase, when progesterone levels are highest (estrogen levels are also elevated at this time), women report reduced positive subjective effects of cocaine (Evans and Foltin, 2006b; Evans et al., 2002; Sofuoglu et al., 1999). Moreover, administration of progesterone attenuates some of the physiological and positive subjective effects of cocaine (Evans and Foltin, 2006a; Sofuoglu et al., 2004). Taken together, these data indicate that the reinforcing effects of cocaine are strongly influenced by a women's hormonal milieu.

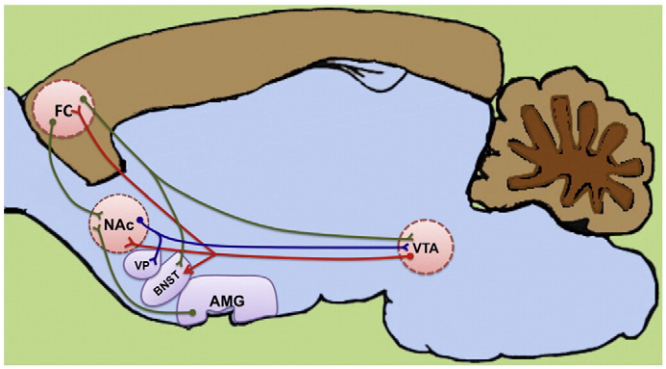

Fig. 1. The human menstrual and rat estrous cycle. The human menstrual cycle (left) occurs over 28 days and is comprised of fluctuating levels of estradiol (E2; top) and progesterone (P4; bottom). Levels of E2 rise to a peak between Days 7 and 14, drop, rise, and then plateau between Days 14 and 28. Progesterone levels rise between Days 0 and 14 from ovulation, reaching their peak at Day 7. The rat estrous cycle (right) is similar but occurs over a 4-day period. Four phases, metestrus, diestrus, proestrus, and estrus comprise the rat estrous cycle. Estrogen levels (top) peak between diestrus (Day 2) and proestrus (Day 1) of the rat estrous cycle, whereas progesterone (bottom) levels reach a peak during the proestrus phase (Day 3).

Animal studies

In preclinical models, the motivational and subjective effects of drugs can be examined using intravenous drug self-administration studies and studies of drug-induced conditioned place preference, respectively (Bardo and Bevins, 2000). Rodent studies have demonstrated sex and hormone related differences in the motivation and subjective effects of drugs of abuse. Specifically, female rats' operant behavior is more robust than males' during acquisition of cocaine and heroin self-administration, escalation of drug intake, and reinstatement of extinguished drug seeking behavior (Lynch and Carroll, 1999; Lynch et al., 2000; Roth and Carroll, 2004). Moreover, female rats acquire intravenous self-administration of cocaine and heroin more quickly and at lower doses than males (Davis et al., 2008; Lynch and Carroll, 1999). In tests of conditioned place preference (CPP), female rats develop CPP at lower cocaine doses than males (Russo et al., 2003b; Zakharova et al., 2009). A recent study from our group was the first to investigate sex differences in drug-primed reinstatement extinguished CPP and found that reinstatement of cocaine CPP is greater for female than male animals (Bobzean et al., 2010). Sex differences in CPP have also been shown for morphine; female rats develop a more robust CPP to lower or much higher morphine doses than males depending upon the strain of rat used in the study (Cicero et al., 2000; Karami and Zarrindast, 2008). These findings reflect the tendency of females to be more responsive to drug-conditioned stimuli than males (Elman et al., 2001; Robbins et al., 1999; Sterling et al., 2004) and may reflect the human condition where women have a higher tendency for relapse into former patterns of drug seeking and taking behaviors.

Ovarian hormones

The observed sex differences in motivational and subjective effects of drugs of abuse are thought to be due to the activational effects of ovarian hormones. This notion is supported by studies assessing the behavioral response to drugs over the course of the estrous cycle. The majority of these studies have been conducted using cocaine as the drug of abuse. Phase of the estrous cycle has been shown to influence an animal's motivation to self-administer cocaine (Roberts et al., 1989) as well as the intensity of cocaine-induced stereotypic and locomotor activities (Quinones-Jenab et al., 1999). Moreover, the psychomotor effects of cocaine and self-administration are higher during estrus compared to other phases of the estrous cycle (Quinones-Jenab

et al., 1999; Roberts, 1989; Roberts et al., 1989). The notion that ovarian hormones are important for differences in reinforcing properties of drugs are further supported by research using ovariectomized (OVX) rodents which has consistently demonstrated a key role for estradiol (E2) in enhancing the responsivity to cocaine in females (Becker, 1999; Festa et al., 2004). More specifically, removal of endogenous estrogen (and progesterone) by OVX decreases acquisition rates of cocaine self-administration and cocaine-primed reinstatement of cocaine-seeking behavior and replacement of E2 restores cocaine self-administration rates to levels comparable with intact controls (Frye, 2007; Larson et al., 2005; Lynch et al., 2001). Administration of progesterone to OVX rats attenuates cocaine seeking behavior, cocaine-induced locomotor sensitization and blunts estradiol-augmented increases in cocaine sensitization (Becker, 1999; Jackson et al., 2006; Niyomchai et al., 2005; Russo et al., 2003a; Sircar and Kim, 1999). In studies of opioid drugs, E2 treatment to ovariectomized (OVX) rats caused faster acquisition of heroin self-administration and greater heroin consumption (Roth et al., 2002). Further, OVX animals demonstrated a reduced preference (CPP) for morphine associated cues and E2 treatment facilitated morphine CPP in a dose dependent manner (Mirbaha et al., 2009).

In summary, the majority of studies reveal that E2 plays an important role in sex differences in the behavioral response to drugs of abuse (Festa and Quinones-Jenab, 2004). However, it should be noted that in studies of humans and non-human primates, some authors suggest that it is not the enhancing effects of E2 but the attenuating effects of progesterone that strongly influence the rewarding properties of psychostimulants (Evans and Foltin, 2010).

Mesolimbic reward circuitry

It has been long known that dopamine (DA) is important for reinforcement and motivation of actions. However most of what we know about DA, reinforcement and motivation comes from studies of male animals. For the purposes of this review, we will review the literature on the mesolimbic DA system as it is collectively dogmatized and add in where females have been shown to demonstrate structural and functional differences. Almost sixty years ago, Olds and Milner reported that male rats would press a lever to receive electrical stimulation in particular areas of the brain: intracranial self-stimulation (Olds and Milner, 1954). Subsequent studies over the following two decades revealed that it was stimulation of dopamine (DA) axons in the medial forebrain bundle that was essential for intracranial self-stimulation reward (Olds, 1969; Ungerstedt, 1971; Ungerstedt et al., 1974). Since then, advances in techniques such as neuroimaging, animal models, and biochemical immunoassays have produced converging evidence for a specific functional neuroanatomical pathway of reward, known as the mesolimbic DA pathway.

Overview of the mesolimbic dopamine system

The mesolimbic pathway originates with A10 DA cell bodies in the ventral tegmental area (VTA) which project to the nucleus accumbens (NAc), bed nucleus of stria terminalis (BNST), and frontal cortex (Gardner, 2011; Koob, 1992). Neural activity in both the VTA and NAc is modulated via GABAergic, glutamatergic, serotonergic, and opioid peptidergic systems. The VTA also receives noradrenergic input from the locus coeruleus (Hyman et al., 2006; Koob, 1992; Volkow et al., 2004; Wise, 2004). Administration of drugs of abuse and/or exposure to drug conditioned stimuli results in activation of the mesolimbic DA pathway via stimulation of VTA DA release into the NAc (Di Chiara and Imperato, 1988; Owesson-White et al., 2009; Phillips et al., 2003; Pierce and Kumaresan, 2006) (Fig. 2).

Addiction: dysregulation of the dopamine system

Normally, DAergic transmission within this circuit plays a critical role in modulating the flow of information through the limbic system to modulate naturally rewarding motivated behaviors such as feeding, drinking, sexual behavior, maternal and paternal behaviors, and social interactions (Gardner, 2011); however, chronic enhanced activation of mesolimbic DA transmission by drugs of abuse can result in long-term functional changes within this pathway. One consequence of repeated persistent increases in extracellular DA in the NAc is a sensitized increase in DA neurotransmission which is postulated to cause consequent morphological and functional changes in mesolimbic reward neurocircuitry (Hedges et al., 2010). For example, administration of psychostimulant drugs (cocaine and amphetamine) leads to increased dendritic branching of NAc medium spiny neurons (Robinson and Kolb, 1997, 1999a). Interestingly, other drugs of abuse such as morphine have been shown to induce morphological changes in the same neurons but in the opposite direction; resulting in a decrease in dendritic complexity (Robinson and Kolb, 1999b). These neuroadaptations have been shown to cause hypersensitivity to drug-associated stimuli (Di Chiara et al., 1999; Everitt and Wolf, 2002; Nestler, 2002a,b). With long-term exposure to a drug of abuse, persistent neuroadaptations in the mesolimbic DA system can manifest an enduring neurobiological vulnerability to relapse in some individuals.

Sex differences in striatal dopaminergic function

Dysregulation of the DA pathway by drugs of abuse is influenced by sex which has been supported by both human (although somewhat limited) and animal studies. For example, Laakso et al. (2002) report that premenopausal women have higher presynaptic DA synthesis capacity in the striatum compared to men (Laakso et al., 2002). In another study, men show more basal DA release in multiple regions of the striatum compared to women (Munro et al., 2006). Furthermore, evidence suggests that women may have lower striatal D2 receptor affinity than men and these differences appear to be affected by age and menstrual cycles (Pohjalainen et al., 1998). Considered together, the evidence presented here, although limited, indicates sex dependent dimorphisms in the mesolimbic DA system functioning, implicating a role for ovarian hormones in the psychopathology of addiction.

More numerous and extensive investigations of sex differences in DAergic function have been conducted using animal models. Rodent studies have shown that in the striatum there are clear sex differences in basal DAergic tone and activation following the administration of drugs of abuse (reviewed in Becker, 1999; Becker and Hu, 2008; Becker et al., 2012). Female rats have greater levels of basal and K^+ stimulated DA concentrations in the striatum than males (Castner et al., 1993; Walker et al., 2000) and greater striatal concentrations of DA following cocaine administration (Walker et al., 2006). The sexually dimorphic patterns of the DA system are likely largely due to the influence of fluctuating levels of ovarian hormones associated with the human menstrual and rodent estrous cycles (Fig. 1). Preclinical microdialysis experiments support this showing that basal NAc levels of DA and its metabolite, DOPAC, are modulated by the estrous cycle in female rats (Shimizu and Bray, 1993). Moreover, ratios of extracellular levels of striatal DOPAC/DA are highest during proestrus, suggesting a greater magnitude of DA turnover when circulating levels of estrogen are high compared to other phases of the estrus cycle when estrogen is low (Xiao and Becker, 1994). Together these data provide support for the hypothesis that fluctuations in levels of ovarian hormones over the estrous cycle of female rodents correspond with alterations in DA system activation.

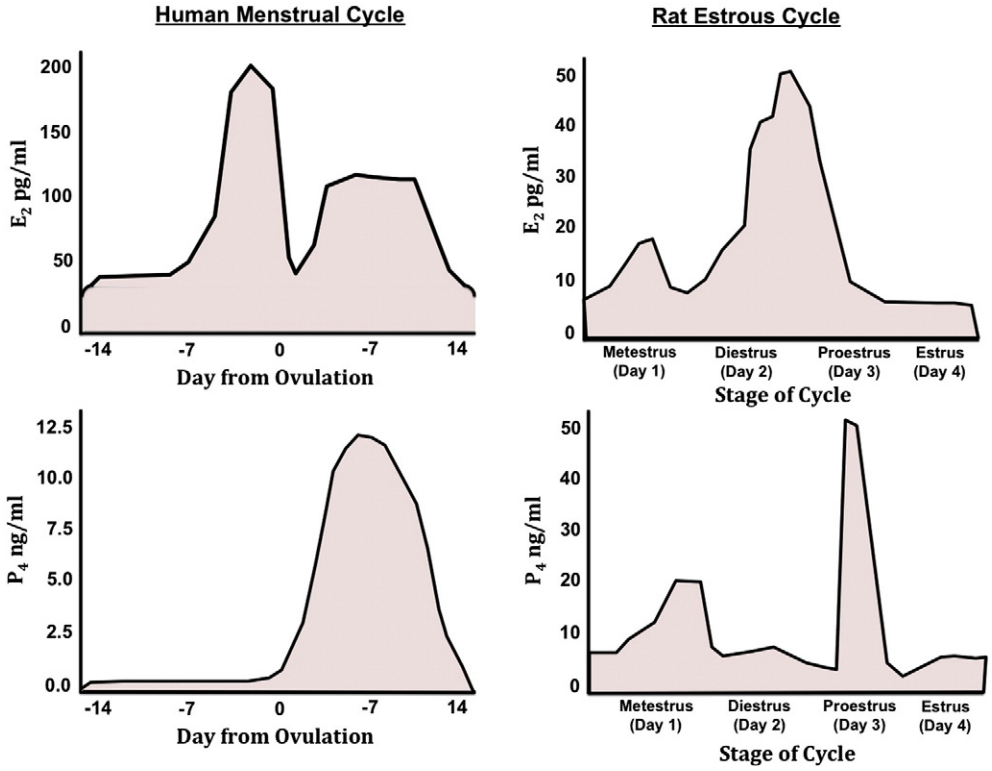

Fig. 2. Mesolimbic reward circuits. The mesolimbic pathway originates with dopaminergic cell bodies in the VTA. Dopamine (red) cell bodies in the VTA are tonically inhibited by GABAergic neurons in the VTA. This pathway projects primarily to the NAc, but there are also projections to the BNST, and frontal cortex. Both the VTA and NAc are modulated by rich innervation from GABAergic (blue) and glutamatergic systems (green).

Estradiol

Several lines of preclinical evidence demonstrate the modulation of the neurochemical activities in midbrain DA systems by E2 (Becker, 1990; Becker and Beer, 1986; Bitar et al., 1991; Di Paolo et al., 1985). In fact, E2 affects both pre- and postsynaptic components of DA transmission (Becker and Beer, 1986; Van Hartesveldt and Joyce, 1986). For example, an acute injection of E2 has been shown to increase striatal DA release and turnover (Becker and Beer, 1986; Becker and Ramirez, 1981; Becker et al., 1984; Di Paolo et al., 1985) and increase the density of striatal DA uptake sites (Morissette et al., 1990). Postsynaptically, the effects of E2 are documented as increases in numbers of striatal D1 DA receptors, decreases in high affinity agonist D2 DA binding, and increases in low affinity D2 DA agonist binding (Di Paolo et al., 1985; Levesque and Di Paolo, 1988, 1989; Morissette et al., 1990; Shieh and Yang, 2008). Presynaptic effects of E2 were demonstrated in studies showing E2 potentiated amphetamine-induced DA release and enhanced DA turnover in the NAc (Becker et al., 1984; Di Paolo et al., 1985; Thompson and Moss, 1994). Furthermore, E2 promotes the sensitivity of VTA DA neurons to cocaine (Zhang et al., 2008) and enhances cocaine-stimulated striatal DA release (Peris et al., 1991). Lastly, repeated cocaine administration to E2-treated OVX rats results in decreases in striatal D2/D3 (Febo et al., 2003). These potentiative effects of E2 on striatal DA activity are, in part, responsible for the sex and hormone-related differences in subjective and physiological responses to cocaine (Becker and Ramirez, 1981; Becker and Rudick, 1999; Quinones-Jenab, 2006; Walker et al., 2001).

Facilitation of the reinforcing effects of drugs of abuse may be attributed to the interactions between DA receptors and estrogen receptors. In fact, midbrain DA systems also contain high numbers of estrogen alpha (ERα) and beta receptors (ERβ) (Creutz and Kritzer, 2002, 2004). Consequently, evidence suggests that E2 regulation of D2 striatal DA receptors occurs through the activation of the ERβ (Morissette et al., 2008). Chronic E2 administration increases dorsal and ventral striatal D1 receptor density and binding through activation of the ERβ (Di Paolo, 1994; Lammers et al., 1999; Landry et al., 2002; Le Saux et al., 2006; Levesque and Di Paolo, 1989; Zhou et al., 2002); implicating E2 activation of the ERβ in the upregulation of DA receptors in the NAc. Studies in male animals have demonstrated that the upregulation of these DA receptors is critical for reinstatement of drug seeking behavior (Anderson and Pierce, 2005). Studies in our lab have demonstrated that reinstatement of cocaine CPP is more pronounced in female rats (Bobzean et al., 2010); the above evidence for ERβ induced the upregulation of NAc DA receptors could provide a potential mechanism for this finding. In addition, E2 produces indirect effects at D1 receptors. More specifically, changes in levels of E2 regulate the firing rate of DA neurons, cause changes in DA release, and changes in DA D1 receptor density in both the dorsal striatum and NAc (Becker, 1999; Becker and Rudick, 1999; Dazzi et al., 2007; Di Paolo, 1994; Lammers et al., 1999; Landry et al., 2002; Levesque and Di Paolo, 1989; McEwen and Alves, 1999; Peris et al., 1991; Zhou et al., 2002). Thus, estradiol-induced activation of the ERβ in the NAc is involved in the upregulation of DA receptors. The upregulation of these DA receptors is critical for changes in DA mediated behaviors.

Intracellular mechanisms of addiction: CREB, Fos, and ERK

Drugs of abuse affect several intracellular responses in the NAc including 3′–5′cyclic AMP (cAMP), protein kinase A (PKA) and mitogen-activated protein kinase (MAP kinase) pathways, which are involved in regulation of many cellular processes (Borgkvist and Fisone, 2007; Carlezon et al., 1998; Hyman et al., 2006; Jones and Bonci, 2005; Konradi et al., 1994; Nestler, 2002a,b; Olson et al., 2005; Walters and Blendy, 2001; Walters et al., 2003; Wolf et al., 2003). Induction of these signaling cascades can stimulate the activity of transcription factors such as Fos and cyclic AMP response element binding

protein (CREB) which, in turn, may mediate dendritic spine formation and long-term cellular plasticity (Dietz et al., 2009). Activation of these pathways can originate from G-protein coupled receptor, ionotropic glutamate receptor, and growth factor receptor activation. Binding of these receptors stimulates a cascade of phosphorylation events. For example, NAc DA receptor activation induces CREB through a PKA-dependent intracellular mechanism (Brami-Cherrier et al., 2002; Culm et al., 2004; Das et al., 1997; Dudman et al., 2003; Pierce and Kalivas, 1997; Yan et al., 1999). The phosphorylated form of CREB (pCREB) regulates the expression of several genes important to brain reward function (McClung and Nestler, 2003). Furthermore, there is evidence that CREB induction contributes to cocaine's induction of dendritic spines on NAc medium spiny neurons in male animals (T.E. Brown et al., 2011).

Drugs of abuse also induce extracellular signal-regulated kinase (ERK) in the striatum. ERK belongs to the family of MAP kinases which are involved in regulation of many cellular processes (Kyosseva, 2004). Within the mesolimbic circuit, ERK responds to DA and glutamate receptor stimulation and its activation is mediated, in part, by the actions of cAMP and PKA (Morozov et al., 2003). The regulation of drug-induced gene expression by DA and glutamate (NMDA) receptors is dependent upon ERK activation (Valjent et al., 2005; Zhang et al., 2004). In addition, its important role in activation of the transcription factors CREB, Fos, and ERK signaling has been shown to play a role in drug reward and to be a critical regulator of structural remodeling of dendrites and spines of medium spiny neurons in the striatum of male animals (Lu et al., 2006; Miller and Marshall, 2005; Zhang et al., 2012).

Another prominent cellular response to the effects of drugs of abuse on the DA receptor is the upregulation of Fos family proteins in the mesolimbic system. Acute exposure to drugs of abuse causes the transient induction of c-Fos and FosB (Graybiel et al., 1990; Hope et al., 1992; Perrotti et al., 2008; Young et al., 1991), while chronic exposure to drugs causes the accumulation of a stable truncated splice variant of the *fosB* gene, ΔFosB (Hiroi et al., 1997; Hope et al., 1994; Moratalla et al., 1996; Nye et al., 1995; Perrotti et al., 2005, 2008; Pich et al., 1997). Because of its stability, ΔFosB not only accumulates, but also persists long after drug administration has ceased (Nestler et al., 2001; Perrotti et al., 2005). ΔFosB is thought to activate genes that increase the user's sensitivity to the effects of the abused drug (Colby et al., 2003; Kelz et al., 1999; Nestler, 2001). As such, ΔFosB is often studied as a mediator of long-term structural and functional changes within the reward circuitry of the brain (Nestler et al., 2001).

Over the past decade, sex differences in basal and drug activation of the cAMP and PKA pathways in the NAc have been documented. However, to date most of these studies have been done solely using psychostimulants. For example, compared to males, drug naive, saline, and cocaine treated females have higher NAc levels of PKA protein and phosphorylated DARPP-32 protein at the PKA site (Lynch et al., 2007; Nazarian et al., 2009). These data are further validated by similar evidence showing that males and females have different basal and cocaine induced levels of accumbal pERK, delta Fos B, and pCREB (Nygard et al., 2013). These data point to a role for E2 in modulating drug induced activation of these systems and the subsequently morphological and functional changes associated with long-term cellular plasticity.

A small number of recent studies have shown hormonal modulation of cAMP and PKA pathways. For example, the activity of various intracellular signaling cascades fluctuates with the estrous cycle in the NAc of cocaine treated intact females and saline controls (Weiner et al., 2009). Attempts to clarify the specific role of E2 on these intracellular signaling cascades have used OVX females. The results of one study show that OVX females treated with E2 demonstrate E2 induced initiation of PKA cascades and CREB protein phosphorylation via activation of G-protein dependent cell signaling cascades (Hammes and Levin, 2007). Work in Dr. Catherine Woolley's lab has demonstrated that the downstream effect of these results is likely contributing to the structural sexual dimorphism seen in dendritic morphology and spine density (Forlano and Woolley, 2010; Wissman et al., 2011, 2012). In light of these findings, research investigating the experimental manipulation of estrogen receptors in OVX female rats is receiving increased attention. However, further research is still needed to fully understand the functional interplay between ovarian hormones and drug associated activation of these pathways and their relationship to long lasting changes in neurocircuitry and behavior.

Ventral tegmental area

Although the sex differences and the effects of ovarian hormones on the mesolimbic DAergic system is best characterized in the striatum, there are also sex and estradiol-mediated differences in DA cells in the VTA (Gillies and McArthur, 2010; Johnson et al., 2010; Morissette et al., 2008). As previously stated, the VTA is an important mesolimbic structure containing neurons that project DA to areas of the forebrain that control motivation and reward-seeking behavior. Females have a significantly greater proportion of VTA DAergic neurons compared to males (Kritzer and Creutz, 2008). In a study that examined the effects of E2 on immunoreactivity for tyrosine hydroxylase (the rate-limiting enzyme for DA synthesis) OVX reduced the number of tyrosine hydroxylase-immunoreactive (TH-IR) cells in the VTA while E2 replacement prevented this cell loss in female mice and rats (Johnson et al., 2010). This loss of TH cells due to OVX and subsequent augmentation after E2 treatment demonstrates that E2 is required for the survival of TH-IR cells in the VTA of female rats (Johnson et al., 2010). Other experiments investigating the effects of E2 on VTA DA transmission report that the basal firing rate, bursting rate, and spontaneous activity of VTA DA neurons is lowest in proestrus females but increases during estrus. Cocaine's known inhibitory effect on VTA DA cell firing (Cameron and Williams, 1994) is responsible for maintaining sensitivity of DA cells. This effect is stronger in females during proestrus compared to estrus (Zhang et al., 2008). Additionally, OVX blocked the inhibitory effect of cocaine on VTA DA neuron firing while E_2 replacement therapy restored it (Zhang et al., 2008). In summary, E_2 plays a critical role in preserving the sensitivity of VTA DA neurons.

Negative reinforcement, opponent process and neural stress systems

The loss of control over drug seeking and intake is not just a product of the positive reinforcing properties of drugs and drug-related stimuli; drug-seeking and taking behaviors are also elicited via negative-reinforcement motivation (Gardner, 2011; Koob et al., 2014). This concept of a shift in motivation and neural systems is used to explain the characteristic persistent changes in motivation that are associated with drug dependence in states of addiction (Koob and Le Moal, 2001, 2008). This reflects changes in activity of midbrain–forebrain systems specifically, from impulsive to compulsive use, which represents a shift from prefrontal regulatory control of behaviors to limbic/striatal control (Everitt and Robbins, 2005; Piazza and Deroche-Gamonet, 2013). Under this model of negative reinforcement motivation, the primary motivation for drug use is to self-medicate internal distress states that may be the result of pre-existing basal aversive states (anxiety disorders, depression), or those which exist as the result of withdrawal from the drug (including symptoms such as dysphoria, anxiety, irritability, and sleep disturbances). This shift is heavily dependent on the neuroadaptive changes in neurocircuitry and reward processing as previously discussed, in addition to a functional recruitment of the brain stress systems.

Stress

Typically, a stressful event triggers a stress response that elicits the activation of the hypothalamic–pituitary–adrenal (HPA) axis. Briefly,

neurons in the paraventricular nucleus of the hypothalamus (PVN) release corticotrophin releasing factor (CRF) and vasopressin into the anterior pituitary gland to stimulate the synthesis and release of adrenocorticotropic hormone (ACTH). This, in turn, stimulates both synthesis and release of glucocorticoids (cortisol in humans; corticosterone in rats and mice) from the adrenal glands into general circulation to elicit an appropriate stress response. The presence of increased levels of glucocorticoids produces an inhibitory effect (negative feedback) on the stimulatory limb of HPA axis. In a similar fashion, acute administration of most drugs of abuse activates the HPA brain stress pathway (Sinha, 2008). Data from both human and animal studies demonstrate that regular and chronic drug use in addition to states of drug withdrawal and abstinence are associated with dysregulation of the CRF-HPA system (for review, see Sinha, 2008).

The same types of stress that trigger activation of the HPA axis have also been shown to stimulate initiation of drug use, increase current drug use, and induce relapse to former patterns of compulsive drug taking (Koob, 2009; Sinha, 2008). Rodent preclinical and human studies have also shown blunted HPA axis responses to stress challenge with long term drug use (Adinoff et al., 2005; Kreek, 1997). Not surprisingly, HPA axis dysfunction has been reported in substance use disorders (Gerra et al., 2008; Walter et al., 2006). In particular, a high prevalence of adrenal insufficiency has been reported in opiate-dependent subjects (Cooper et al., 2003; Tennant et al., 1991). A study of male heroin users in various stages of detoxification revealed that hypocortisolism was directly related to the amount of heroin consumed, and indirectly associated with the amount of time since the last heroin administration (Cami et al., 1992). Numerous clinical and preclinical studies have demonstrated sex differences in HPA axis activation. Overall, these studies show that females have higher levels of circulating cortisol, greater ACTH release in response to stress, faster onset of cortisol secretion after stress, and a faster rate in the rise of cortisol (Armario et al., 1995; Haleem et al., 1988; Handa et al., 1994; Heinsbroek et al., 1991; Jones et al., 1972; Kant et al., 1983; Kitay, 1961, 1963; Le Mevel et al., 1979; Rivier, 1999; Yoshimura et al., 2003; Young, 1996). Though testosterone has been reported to suppress activation of the HPA axis in male rats (Handa et al., 1994), in general, these sex differences in HPA axis regulation are attributed to the activational effects of ovarian hormones in females.

Effects of sex and ovarian hormones on HPA functioning

Fluctuating levels of ovarian hormones exert modulating effects on HPA axis functioning, including responsiveness and sensitivity to negative feedback (Young, 1995). Female rats have prolonged secretion of ACTH as well as increased corticosterone production during the proestrus phase of the estrous cycle, a phase of the cycle when circulating estrogen and progesterone levels are highest, compared to the diestrus phase of the cycle, a phase when levels of these hormones are lower (Viau and Meaney, 1991). They are also insensitive to the feedback effects of exogenously administered corticosterone on stress induced ACTH secretion; additionally, OVX increases the sensitivity of steroid feedback (Young, 1996). Similarly, women are less sensitive to dexamethasone feedback during the luteal phase of the menstrual cycle than during the early follicular phase (Altemus et al., 1997), suggesting that both estrogen and progesterone influence this insensitivity to glucocorticoid feedback in females (Burgess and Handa, 1992; Ferrini et al., 1995; Patchev et al., 1995; Rousseau et al., 1972). Hormone replacement studies have produced conflicting evidence. While some studies demonstrate that E2 enhanced onset and prolonged ACTH and corticosterone activity in female rats following stressful stimulation (Burgess and Handa, 1992; Carey et al., 1995; Viau and Meaney, 1991), other studies have shown an inhibitory effect of E2 treatment (Russell et al., 2013; Young et al., 2001). The difference in these results is likely due to differences in hormone replacement dosing and treatment regimens. Despite the conflicting evidence in the literature, ovarian hormones consistently show modulation of HPA axis stimulation and sensitivity and this, in turn, likely influences reward processing and addiction (Handa et al., 1994).

Anti-reward pathway

The neural entity known as the extended amygdala is a major component of the extra-hypothalamic CRF system that is associated with negative reinforcement mechanisms (Fig. 2) (Koob, 2010; Koob and Le Moal, 2005). The neural circuits and neuropharmacological mechanisms which comprise the extended amygdala are involved in the acute reinforcing actions of drugs of abuse (Koob et al., 1998) and also play an important role in the changes in the reward system associated with dependence (Koob, 2003a). The extended amygdala is the key anatomical substrate that comprises the so called “anti-reward pathway” which includes the central nucleus of the amygdala (CeA), bed nucleus of stria terminalis (BNST), and a transition zone in the medial (shell) of the nucleus accumbens (NAc Shell) (Heimer and Alheid, 1991) Figure 3. All of these regions share cytoarchitectural and circuitry similarities (Heimer and Alheid, 1991). The extended amygdala receives numerous afferents from limbic system structures, such as the basolateral amygdala and hippocampus, and sends efferents to the medial part of the ventral pallidum and also a large projection to the lateral hypothalamus (Heimer and Alheid, 1991; Koob, 2003a; Koob et al., 1998).

Central nucleus of the amygdala

Within the neurocircuitry of the extended amygdala, additional neurochemical systems are engaged to overcome the continued perturbing presence of a drug of abuse and to restore normal function. For example, increases in extracellular levels of CRF in the CeA are observed during withdrawal from ethanol, opiates, cocaine, and delta-

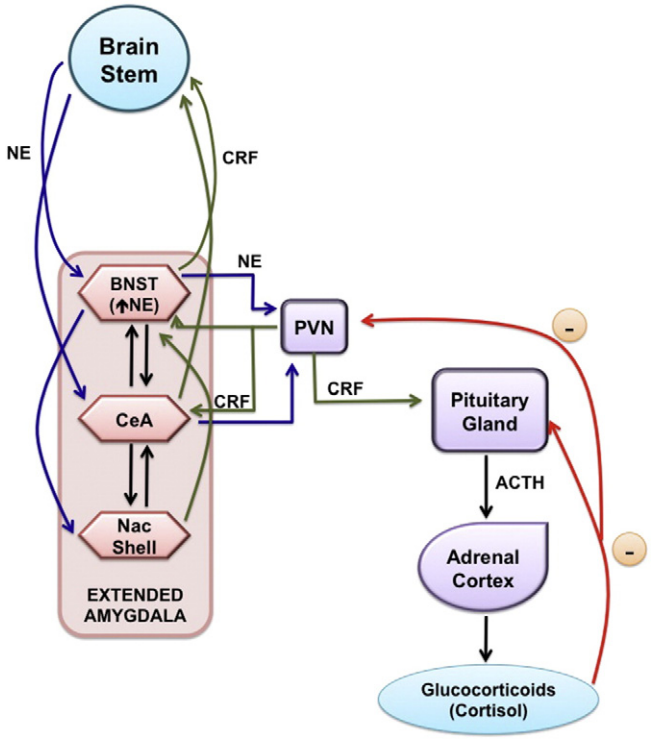

Fig. 3. Schematic overview of the interface among the HPA-axis and extended amygdala. The extended amygdala is comprised of the central amygdala (CeA), bed nucleus of stria terminalis (BNST) and the nucleus accumbens shell (NAc Shell). This circuit receives corticotropin releasing factor (CRF) from the paraventricular nucleus of the hypothalamus (PVH) and norepinephrine (NE) from pontine nuclei in the brainstem.

9 tetra hydrocannabinol (THC) (Koob, 2003a). Moreover, in drug-dependent male animals, the recruitment of CRF activity seems to serve a motivational role in that CRF and NA receptor blockade reduce the motivational effects of drug withdrawal (Delfs et al., 2000; Heinrichs et al., 1995; Schulteis et al., 1994). Further, extracellular CRF is increased in the CeA during acute drug withdrawal (George et al., 2007; Maj et al., 2003; Merlo Pich et al., 1995; Richter and Weiss, 1999; Rodriguez de Fonseca et al., 1997; Zorrilla et al., 2012). The CeA sends a CRF-containing projection to the BNST that appears to be critical for stress-induced reinstatement to drug seeking behavior in male animals (Erb et al., 2001). A CRF mechanism seems to be responsible for the dysregulation of the intrinsic excitability observed in some BNST neurons after protracted withdrawal from cocaine, heroin, and alcohol (Francesconi et al., 2009). Despite the large sexual dimorphisms in regulation of the HPA axis, the vast majority of research on CRF and addiction has been done in males.

BNST

The BNST plays an essential role in the modulation of the stress response and in the long-term actions of drugs of abuse (Aston-Jones et al., 1999; Delfs et al., 2000; Epping-Jordan et al., 1998; Georges and Aston-Jones, 2001; Koob, 2003b). In addition, the BNST is a critical mediator of stress-induced reinstatement of cocaine self-administration in male animals (Shaham et al., 2000). Extracellular levels of CRF are increased in the BNST during ethanol withdrawal, and such increases are reduced by subsequent ethanol intake (Olive et al., 2002). Interestingly, studies also show that inactivation of the BNST reduces both stress- and cue-induced reinstatement to drug seeking (Buffalari et al., 2012). Catecholamine-mediated activation of the BNST is critical for reinstatement of drug seeking behavior (Pacak et al., 1995). Locally, intra-BNST injections of CRF induce reinstatement (Erb and Stewart, 1999), while intra-BNST infusion of CRF receptor antagonists blocks stress-induced reinstatement (Erb and Stewart, 1999; Wang et al., 2006). ICV injections of NE induce reinstatement of cocaine self-administration and increase cellular activity in the BNST as measured by *cfos* mRNA (Z.J. Brown et al., 2011). Additionally, blockade of β-adrenergic receptors in the BNST reduces reinstatement of cocaine self-administration (Leri et al., 2002).

Sex differences in CeA and BNST

Sexual dimorphisms in the CeA and BNST and gonadal hormonal regulation of CRF (Bangasser and Valentino, 2012) can increase stress in females making them more vulnerable to certain aspects of drug addiction. However, the majority of studies on CRF/extended amygdala regulation and addiction have been done in males, so our knowledge of CRF-extended amygdala–drug abuse interactions in females is extremely limited. The few studies that do exist implicate both CRF-HPA and extra-hypothalamic CRF systems in augmenting the responses of females. For example, female rats demonstrate greater pharmacological stress-induced reinstatement of cocaine seeking behavior (Anker and Carroll, 2010; Feltenstein et al., 2011) and potentiated longer lasting stress-induced behavioral and NAc DA neurochemical cross-sensitization (Holly et al., 2012). Moreover, females are less sensitive to depressive effects of kappa opioid receptor antagonism and the BNST and PVN are the likely sites of action (Russell et al., 2013).

Anti-reward and opponent processes

As explained through the theory of opponent process of addiction, an allostatic state is driven by a dysregulation in the brain circuits within the extended amygdala (Koob and Volkow, 2010). Changes within this neural substrate are thought to modulate the net hedonic effects (a-process) of drugs, as well as changes in the counter-adaptive (b-process) process that counteract this response. It has been recently proposed that changes in a-processes occur within the mesolimbic DA system, whereas alterations in b-processes occur as between-system changes that are modulated via CRF stress systems (George et al., 2012). In this way, the within system processes gradually compromise and attenuate the positive reinforcing properties of the drugs. In this state of diminishing reward, the user will likely continue to consume increasing amounts of drug in an effort to re-experience earlier states of positive reinforcement and combat the decreased function of a-processes. The hedonic states induced by drugs of abuse also activate between system changes in brain–stress systems in the extended amygdala that sensitize with repeated drug exposure and drive negative reinforcement (Edwards and Koob, 2010; George et al., 2012).

Dr. Laura O'Dell has recently proposed that females display stronger positive effects (a-process) to drugs of abuse (specifically nicotine) that will recruit stress systems (b-process) to a larger extent than males (O'Dell and Torres, 2014). This hypothesis is based on the large body of clinical and epidemiological evidence along with extensive work conducted in Dr. O'Dell's own lab using adolescent and adult male and female animals in the area of nicotine addiction. According to this hypothesis, females exhibit a larger recruitment of opponent process systems during long-term nicotine use which results in a greater stress response during nicotine withdrawal as compared to males (O'Dell and Torres, 2013). An excellent detailed description of the theory of a more rapid downward spiral into drug abuse for females is provided in Becker et al. (2012).

Together, the findings reviewed above indicate that the neural circuits and neuropharmacological mechanisms associated with the CRF-HPA and extended amygdala likely represent common anatomical substrates for acute drug withdrawal syndromes and the negative effects of compulsive drug administration on reward function (Koob et al., 1998). Adaptations in these systems may represent the transition between controlled to compulsive drug seeking and use. Importantly, these neuroadaptations are sex specific. While, the aversive and/or negative emotional states that drive negative reinforcement in addiction are often the result of a shift from positive reinforcement driving the motivated behavior to negative reinforcement driving the behavior (Koob and Le Moal, 2005), it is also frequently the case that negative affective states precede drug-taking behaviors especially in women (Zilberman et al., 2003a,b). For example, psychological stress can produce drug craving and increase the risk of drug relapse (Sinha, 2001). Clinical studies, anecdotal evidence, and laboratory-based studies have identified both stressors and drug-related environmental cues as being among the most important facilitators of drug reinstatement and seeking in animals and humans. Moreover, the studies above provide evidence to support opponent processes and anti-reward/stress circuitry as addiction is not simply due to a growth of tolerance to the drugs being abused (due to decreased DA release with drug seeking and taking), but it is also due to increased internal distress caused by a sensitization of the arousal/stress circuits of the brain that require more drug to momentarily quell the internal distress. However, limited data exist regarding the suitability of this model to female addicts.

Summary/conclusions

Males and females differ in their magnitude of response to various properties of drugs of abuse. It is likely that the molecular neuroadaptations, which develop over the course of addiction, contribute to female increased sensitivity to drug-associated cues and stress that influence individual vulnerability to drug addiction and relapse. Furthermore, it is becoming increasingly apparent that females are more susceptible to the negative reinforcing motivation to seek and take drugs than males. Estrogen has been consistently shown to facilitate drug taking and motivation for drug reward by interacting with reward- and stress systems. Still, more research is needed to elucidate

sex and hormonal influences on addiction-mediated dysregulation of reward and stress (anti-reward) neural circuitry.

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