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Sex differences in vulnerability to addiction

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Abstract

This article reviews the evidence for sex differences in vulnerability to addiction with an emphasis on the neural mechanisms underlying these differences. Sex differences in the way that the gonadal hormone, estradiol, interacts with the ascending telencephalic dopamine system results in sex differences in motivated behaviors, including drug seeking. In rodents, repeated psychostimulant exposure enhances incentive sensitization to a greater extent in females than males. Estradiol increases females' motivation to attain psychostimulants and enhances the value of drug related cues, which ultimately increases their susceptibility towards spontaneous relapse. This, along with females' dampened ability to alter decisions regarding risky behaviors, enhances their vulnerability for escalation of drug use. In males, recent evidence suggests that estradiol may be protective against susceptibility towards drug-preference.

Sex differences in the actions of estradiol are reviewed to provide a foundation for understanding how future research might enhance understanding of the mechanisms of sex differences in addiction-related behaviors, which are dependent on estradiol receptor subtype and the region of the brain they are acting in. A comprehensive review of the distribution of ERα, ERβ, and GPER1 throughout the rodent brain are provided along with a discussion of the possible ways in which these patterns differentially regulate drug-taking between the sexes.

The article concludes with a brief discussion of the actions of gonadal hormones on the circuitry of the stress system, including the hypothalamic pituitary adrenal axis and regulation of CRF. Sex differences in the stress system can also contribute to females' enhanced vulnerability towards addiction.

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Introduction

This article discusses how drug taking differs between males and females, with a focus on sex differences in the psychostimulants and the transition from initial drug use to repeated chronic abuse, which can make females more vulnerable. “Vulnerability” is defined here as the extent to which an individual is susceptible to experience the neuroplastic changes that result in addiction or addiction-like behaviors. For example, depression, which occurs more frequently in females than males, contributes to increased consumption of drugs of abuse[1,2]. The gonadal hormone estradiol, and estradiol receptor localization, influence motivation for drugs of abuse and in turn can induce neuroplastic changes that result in drug addiction, also referred to as substance use disorder.

Male and female brains differ as a consequence of sexual differentiation during prenatal and postnatal development. The sexually differentiated brain interacts with hormone events in the adult, related to the reproductive cycle in females, for the expression of sex differences in addiction[3]. The developmental path of an individual depends on early exposure to hormones produced by the fetal testes or the absence of these hormones in females. Testosterone produced by the testes, crosses the blood brain barrier, and is converted to estradiol by aromatase[4]. Thus, estradiol is the hormone that plays a primary role in the development, and sexual differentiation, of the brain thereby masculinizing the naïve brain[4] and is important for reproductive function in the adult male brain[5]. In females, without the actions of these gonadal steroids, DNA methylation actively represses the masculinization of DNA, and allows for feminization to occur[6].

Through the actions of estradiol signaling, altered gene expression causes differential patterns of neuronal cell death, growth, and connectivity that have lasting effects on neural circuitry and behavior[7]. For example, in the dorsal striatum, a region implicated in addiction, there are sex differences in the effects of estradiol on dopamine release that are dependent on these developmental processes[8]. In the adult female brain estradiol treatment enhances drug-induced dopamine increases in dorsal striatum and motivation for drugs of abuse[9–11].

The neurobiological differences between males and females prior to drug exposure influence vulnerability to addiction. Addiction has been categorized into different “stages” where there are sex differences in each stage[12]. In women, initiation of drug use is often driven by psychological factors such as anxiety and depression, or after experiencing negative life events; whereas more men report initial drug use in social settings[13,14]. Continued drug use causes sex differences in neuroplastic changes in the reward system and in stress mechanisms in the brain, which contribute to sex differences in drug-seeking after initial use. Women who have sought treatment for addiction report their drug consumption escalated more rapidly than do men in treatment, this phenomenon of rapid escalation of drug use in women is known as “telescoping”[3,15] After escalation of drug use, during maintenance, an individual is constantly thinking about obtaining the next drug dose[3]. With continued use of a drug there is a transition to chronic substance use disorder which is characterized by repeated attempts at abstinence and relapse[16,17]. During abstinence, women report greater craving than do men, which is modulated to some extent by their hormone cycles[18]. Finally, women are more sensitive to environmental cues and report more

spontaneous relapse[19]. One aspect of the environment that is key to sex differences in addiction is activation of the stress axis. After we have discussed sex differences in the neural systems mediating addiction we will return to how the stress system interacts with these systems differentially in males and females to put everything in context.

The neural systems that mediate the transition from casual use to substance use disorder are known as the reward system, as neurons in these regions are activated by endogenous rewards in addition to drugs of abuse. The neural projections from the midbrain regions of the substantia nigra and ventral tegmental areas to the nucleus accumbens, dorsal striatum, amygdala, and prefrontal cortex are key to the development of substance use disorders or addiction. These projections use the neurotransmitter, dopamine, and sex differences in the dopamine-mediated processes of the reward system will be reviewed next.

Sex differences in dopamine-mediated processes

Dopaminergic neurons within the ascending mesotelencephalic pathway are activated in response to adaptive rewarding stimuli, such as food consumption, sexual behavior, and social interactions, all of which are necessary functions for health and reproductive success[20–23]. Drugs of abuse also induce dopamine neurotransmission and sustained drug use causes numerous temporary and permanent physiological changes in the brain[24–29]. The various theories of how dopamine regulates motivated behaviors were developed in male animals. Implications for sex differences in vulnerability and propensity towards addiction are examined next, within the context of these different theories.

The incentive sensitization theory posits that repeated psychostimulant exposure results in sensitization of dopamine neurons which increases ‘wanting’ of the drug.[30]. These neuroadaptations also increase the salience of drug cues which underlie the drive from casual drug use to compulsive drug taking[27,30,31]. Females are more susceptible to incentive sensitization than are males, which may explain the enhanced vulnerability of females’ transition from intermittent drug use to chronic use[32].

Repeated exposure to psychostimulants also causes behavioral sensitization[25,27]. Though both males and females show behavioral sensitization to psychostimulants, females exhibit greater enhancement in rotational movements and stereotyped behaviors (i.e. behavioral sensitization), than males do, after repeated amphetamine or cocaine administration[33–35]. Females also sensitize at lower doses of cocaine than males[36].

Sensitization is regulated by circulating estradiol in females[37–39]. Intact female rodents show varying degrees of behavioral sensitization based on levels of gonadal hormones during their estrous cycle[40–43]. This effect of estradiol to enhance sensitization is not seen in males[37]. Furthermore, testicular hormones do not regulate sensitization in males[38,44]. Thus, sex differences in sensitization of the ascending dopamine system is a candidate to mediate sex differences in the neural mechanisms of addiction.

An alternate theory is the opponent process theory of addiction which proposes that addiction emerges due to avoidance of withdrawal and the related anhedonia[28,45]. In this theory, an initial pleasurable “high” accompanies drug use, which drives motivation for

reuse. Over time sustained drug use results in tolerance to the pleasurable effects of the drug and a transition to increased unpleasant effects of withdrawal. Eventually, motivation for continued use is sustained to avoid the unpleasant effects of drug withdrawal[46].

Women report enhanced negative aspects of withdrawal effects from psychostimulants, along with most other classes of drugs[14,47,48]. The severity of withdrawal is reported to be cyclic with gonadal hormones, suggesting that estradiol is mediating both the positive and negative effects of drug use for women[49]. Unexplained by this theory, however, is the fact that relapse occurs long after drug withdrawal symptoms subside[49,50]. Spontaneous relapse also occurs disproportionally in females compared to males[49]. Thus, while sex differences in withdrawal likely contribute to sex differences in the pattern of drug taking behavior and relapse, the opponent process theory alone is not sufficient to explain all of the sex differences reported in substance use disorders.

Finally, risky decision making is associated with enhanced dopamine release dynamics in the nucleus accumbens shell[51]. Decision-making and risk-taking are related to the choice to consume drugs of abuse. Males are more likely to make “risky” choices in order to receive a higher value reward[52]. Various studies have investigated the role of the ovarian cycle on decision-making in females and reported no effect[52,53]. The stability of females decision making, including their inability to enhance performance on risk-related tasks across training session compared to males, may be due to their hypersensitivity to punishment[54]. On the other hand, ovariectomy increased risky decision making in females, and estradiol reversed this effect, demonstrating that ovarian hormones maintain this sex difference[55]. In women, the sex difference of reduced risk taking may be reflected in the pattern of drug use, where women are more likely to take drugs of abuse or relapse due to stress and lack of social support, compared to men[56].

To summarize, estradiol modulates dopamine-mediated processes that underlie behaviors associated with sex differences in addiction. Estradiol enhances sensitization in females, which is implicated in craving, telescoping of drug use from intermittent to chronic, and relapse to drug-related cues. Estradiol also enhances the negative components of drug withdrawal associated with the opponent process theory of addiction, but decreases risky decision making, both of which may escalate drug use in women.

Estradiol enhances addiction vulnerability in females

Rodents provide an experimental model to study the effect of ovarian hormones on addiction-like behaviors. Similar to humans, the female rat’s ovarian hormones, estradiol and progesterone, vary systematically in a cyclic pattern. The rodent estrous cycle is 4–5 days[57]. During a 14:10 light dark cycle, estradiol reaches its peak during the first half of the light phase of proestrus to trigger the LH surge; progesterone peaks during the second half of the light phase of proestrus to initiate the onset of behavioral receptivity that follows about 6 hours later during the dark phase in association with ovulation and behavioral estrus[57]. During the days after estrus, the follicular phase is re-initiated (metestrus and diestrus) and estradiol and progesterone are lower, with estradiol gradually rising again late during diestrus.

In the laboratory, escalation of drug taking can be measured by the rate at which rodents acquire self-administration of a drug after initial drug exposure. Exogenous estradiol is sufficient to enhance cocaine acquisition in ovariectomized females[58–60]. Estradiol does not facilitate or enhance acquisition of cocaine taking in males[61]. Sex differences in self-administration models are more robust in extended access paradigms versus short or intermittent access paradigms. This suggests that acquisition may be accelerated in females under certain conditions of drug accessibility[62,63]. The escalation of drug use is more difficult to pinpoint in humans, in part, due to changing environmental factors such as drug availability[48]. Historically, drug availability has largely influenced women's use of opiates and psychostimulants as they were prescribed medications or marketing techniques to advance use of these drugs[48].

Under progressive ratio self-administration paradigms, when the "cost" of cocaine is high, females are more motivated to work for cocaine than are males[32]. In intact female rodents, motivation for cocaine is modulated by circulating gonadal hormones and motivation is greatest during periods of the estrous cycle when estradiol is elevated[12,64,65]. This idea is further supported by studies showing ovariectomized adult females without estradiol replacement have lower motivation than those with estradiol[60,66]. Together, these findings suggest that after initial acquisition of drug taking, females are more susceptible to escalate their motivation to attain drug and that this behavioral response of drug-seeking is enhanced by the presence of estradiol.

In rodent models, females in estrus also exhibited greater drug-primed reinstatement compared to females not in estrus and males[67]. Female rodents express signs of enhanced drug craving during estrus compared to non-estrus[68]. In ovariectomized females, estradiol treatment potentiates reinstatement of drug-seeking[65,69,70]. Previous work also suggests that during drug-primed reinstatement, females who are in estrus display greater cocaine-seeking behavior than non-estrous females and males[50]. Further, females take longer to extinguish cocaine-seeking behaviors compared to males[50]. These studies suggest that estradiol plays a role in enhanced drug cravings in females, which may be contributing to the persistence of cocaine-seeking long into abstinence in females and related to the effects of estradiol on sensitization, as discussed above.

Over time, intake of psychostimulants by males also increases, but to a lesser degree than females. Furthermore, males intake does not appear to be regulated by testicular hormones[58]. Males take longer to acquire a condition place preference for cocaine than females and require a higher dose of cocaine to acquire a preference[71]. However, G Protein-coupled estradiol receptor-1 (GPER-1) has been implicated in being protective against development of a preference for cocaine or opioids[72,73]. These findings indicate that estradiol is having opposite effects in males and females on drug-seeking behaviors in rodents. The extent to which this is also true in humans needs to be investigated.

Thus, estradiol is playing an important role in neural processes related to addiction in females, to increase vulnerability. It is also possible that estradiol is acting in males to decrease vulnerability to addiction.

Estradiol Receptors

Estradiol mediates its effects through three receptors: estradiol receptor alpha (ERα), beta (ERβ), and GPER-1. ERα was the first ER to be characterized[74], and until the late 1990s many thought this single receptor mediated all of the functions of estradiol in an uncomplicated fashion. In 1996, researchers recognized ERβ as the second ER[75]. GPER-1, previously known as GPR30, was recognized as an ER in the early 2000's[76]. Collectively these receptors mediate estradiol signaling using both rapid signaling and long-term transcription mediatedresponses. While rapid effects can occur anywhere between a few milliseconds to a few minutes, long-term effects take between a few hours and a few days[77].

Signaling mechanisms of estradiol receptors

The importance of understanding estradiol receptor-mediated signaling cannot be overstated. The outcome of treatment with estradiol will vary depending on the receptor's identity, location, function, and mechanism of action. ER signaling relies on four basic mechanisms: genomic, tethered, nongenomic (including caveolin-associated ERα and ERβ), and ligand-independent [Figure 1]. Genomic and tethered mechanisms occur within the nucleus, while non-genomic and ligand-independent mechanisms are extranuclear.

To mediate direct genomic effects, both ERα and ERβ can act as ligand-activated transcription factors, capable of directly affecting gene expression by interacting with regions of DNA called estrogen-response elements (ERE), as illustrated in Figure 1A.[78]. As illustrated in Figure 1B., ERα and ERβ can also indirectly affect gene expression. In approximately 35% of the brain regions with ERs the EREs are not available for activation and the effect of estradiol is mediated by other intracellular signaling mechanisms[78–80]. Additionally, through protein-protein interactions, ERα /ERβ signaling can enhance or suppress gene transcription independent of these EREs[81]. Ligand-independent mechanisms that activate the ERE also work in the absence of ER agonists, as illustrated in Figure 1D.

In addition to their actions as separate entities, ERα & ERβ can combine to form a heterodimer with its own distinct effects on transcription[82,83]. ERα and ERβ can function cooperatively in some cells and antagonistically in others[84]. For example, ERβ can directly modulate the activity of ERα by antagonizing ERα dependent transcription[85–88]. Extranuclear ERs can regulate the recruitment of nuclear ERs, plasma membrane bound ERα signaling can affect the activity of nuclear ERα by stimulating phosphorylation as well as facilitating its degradation[89,90]. This mechanism is believed to explain the cyclic changes in the levels of ER-target gene expression[89]. Activation of membrane bound ERs initiates signaling cascades that integrate at the level of the nucleus.

Rapid estradiol receptor signaling

Estradiol signaling can lead to rapid signaling cascades, long-term transcription effects, or both. Either mode of ER signaling can impact the connectivity and function of the brain. ERs associated with the membrane were initially discounted, but it is now recognized that membrane associated ERα and ERβ, along with GPER1, mediate important rapid effects of estradiol and some of these effects are implicated in addiction as discussed below.

Rapid ER signaling can be mediated by classical ERα and ERβ that are palmitoylated and bound to caveolin-1, a structural coat protein, and then trafficked to caveolae, which are invaginations of the plasma membrane that sequester many types of receptors and signaling molecules[91,92]. Caveolin-1 facilitates anchoring these receptors to the caveolae, where estradiol can bind extracellularly and activate associated metabotropic glutamate receptors (mGluR) receptors[93,94]. Multiple mGluRs are associated with ERα and ERβ in the hippocampus and dorsal striatum[95–97]. Rapid ER signaling via mGluRs is implicated in the effects of estradiol on striatal dopamine release and cocaine self-administration[98,99].

Estradiol has been shown to rapidly enhance stimulated dopamine release and down-regulate D2 dopamine receptors in the dorsal striatum *in vitro* and *in vivo*[100–106]. Estradiol also rapidly regulates activity in the nucleus accumbens to affect post synaptic current in medium spiny neurons and stimulated dopamine release[10,107]. These rapid effects of estradiol are implicated in acquisition of cocaine self-administration and motivation for cocaine in females, but not males as discussed above[58,60,61,65].

In the hippocampus and associated circuitry, rapid ER signaling enhances social recognition, episodic memory, as well as object recognition and placement. The mechanism underlying this effect is believed to be the result of estradiol dependent rapid increases in dendritic spines[108–110]. Whether similar ER-dependent changes in spine density is related to vulnerability to addiction remains speculative, but sex differences in cocaine effects on spine density and evoked neural activity in the nucleus accumbens core have been reported[111].

Unlike, ERα and ERβ, GPER-1 is typically an extranuclear receptor embedded in several cell membranes, including the plasma membrane, endoplasmic reticulum, and Golgi apparatus[76,93,112–116]. It can also translocate into the cytoplasm when activated[112]. GPER1 has been reported to enhance memory consolidation acting alone or in collaboration with ERα and ERβ[109,117]. GPER1 may also attenuate vulnerability to addiction in male rodents[73,118].

Localization of Estradiol Receptors

Estradiol has been treated as though it acts uniformly throughout the brain on dopamine activity and addiction-related behaviors, but this is not the case[10,102,119,120]. The types of estradiol receptors and where they are located in the brains of males and females provides potential pharmacological targets and neural locations for hormone-based treatments.

Table I. provides a comprehensive review of whole-brain ER distribution studies normalized such that ER densities can be compared among brain regions[121]. Figure 2. A-C provides a visual comparison of ER densities, according to ER subtype in the rodent brain. Together, these tools provide a way to assess the contribution of ER subtypes within each brain region to addiction vulnerability.

Whole brain ER distribution studies have not found significant sex differences in ER expression, as can be seen in Table 1. Overall, there are limited studies that include both males and females while looking at whole-brain ER expressions, and fewer with the resolution to discern quantitative sex differences. However, studies that examine individual

brain areas do find some sex differences in ERs when assay conditions are enhanced to optimize expression and /or function for a particular brain region. In anatomical studies, it is not possible to discern mechanism of action of the receptors identified, so further research is needed to further determine the functional mechanisms mediating sex differences in many of the brain regions discussed below. Interestingly, while sex differences have not been investigated in all brain regions, there are sex differences in brain regions implicated in drug-taking and addiction.

In the ventral tegmental area, the number of dopamine cells that contained ERβ receptors was small, but males exhibited greater ERβ immunoreactivity in these neurons than females[122]. Intriguingly there were virtually no ERβ immunoreactive cells in the substantia nigra[122]. In the region of the lateral ventral tegmental area known as the parabrachial pigmented nucleus, ERβ-immunoreactivity is found in both dopamine and non-dopamine neurons. Again, the proportion of dopamine neurons with ERβ was greater in males than in females, regardless of stage in estrous cycle, although females in diestrus had fewer ERβ positive neurons than those in proestrus[122]. The dopamine neurons in this brain region have been found to respond to low concentrations of ethanol and so the sex difference in ERβ dopamine neurons may be important for sex differences in addiction[123].

When examining ER expression in midbrain neurons that project to prefrontal cortex in male and female rats, different patterns were found. For males, none of the dopamine neurons labelled as projecting to the prefrontal cortical region contained ERα or ERβ, while in females, some of the dopamine neurons labeled contained ERα, but not ERβ. This proportion of dopamine cells labeled in females was significantly different from males[124]. Thus, ERα and ERβ are strategically located to regulate motivational circuits differentially in males and females.

ERα receptor signaling plays a key role in the sexual differentiation of the mesolimbic reward pathway. ERα knockout animals show sex-specific differentiation patterns in the midbrain. ERα knockout female mice show increased levels of D1 dopamine receptor expression and dopamine receptor-interacting protein 78 (Drip78) mRNA levels[125]. In contrast, ERα knockout males only showed decreased Drip78 mRNA levels[125]. With ERα knockout, both sexes showed reductions in midbrain expression of tyrosine hydroxylase (the enzyme catalyzing the rate limiting step for dopamine synthesis) and brain-derived neurotrophic factor[125]. Overexpression of ERα in dorsal striatum of female rats results in enhanced estradiol-induced motor activity and enhancement of the effect of estradiol to attenuate depolarization induced GABA release[126]. Electron microscope analysis of dorsal striatum finds ERα localized outside the nucleus of GABAergic neurons in female rats[127]. Thus, ERα is playing a role in striatal dopamine function indirectly mediated by rapid signaling through GABA neurons.

ERβis also expressed in striatal regions, consistent with reports that ERβactivation regulates both the neurochemical and behavioral effects of drugs of abuse. In the dorsal striatum, ERβactivation upregulates D2 dopamine receptors[128]. An ERβ agonist induces immediate-early gene c-fos expression in the nucleus accumbens, while an ERα agonist does not[129]. ERβ's regions of action closely align with its alteration of the behavioral effects of a wide

variety of drugs of abuse. Selective activation of ERβ enhances both amphetamine- and cocaine-induced CPP[69,129,130]. ERβ activation, but not ERα, results in enhanced stimulated dopamine release after cocaine in nucleus accumbens shell of females, but not males[10]. Finally, ERβ receptor signaling, but not ERα, mediates estradiol's effect on cocaine-induced reinstatement of extinguished cocaine-seeking behavior in OVX rats[69].

In the cortex, there is a greater expression of GPER1 than in ERα and ERβ, pointing to a role for GPER1 in higher order cognitive functions (Table 1). Importantly, while expression patterns differ, as can be seen in Figure 2, they are also strongly overlapping giving the potential for these receptor mechanisms to interact. Recently, GPER1 has been identified as the first estradiol receptor to modulate the preference for rewarding stimuli in males. A decrease of GPER1 in the CNS, via gene knockout, increases the acquisition of conditioned place preference for morphine in males[73]. Decreasing GPER1 activation in the dorsolateral striatum specifically caused a conditioned place preference for cocaine at a dose that is otherwise not preferred in males. While males and females have similar levels of GPER1 in the dorsolateral striatum, activation may be protective in males while increasing vulnerability in females[72]. GPER1 has also been implicated in enhancing memory consolidation, via enhanced dendritic spine density in the CA1 region of the hippocampus, in female mice[131]. Together, these findings suggest that GPER1 activation could be enhancing memory for environmental stimuli/cues related to a drug-induced state and causing a more rapid formation of conditioned place preference in females, while decreasing these associations in males.

In the next section, the ways in which these sex differences in the neural systems mediating the responses to drugs of abuse interact with the environment will be discussed. The stress system is used as an example of how the environment can trigger neural responses in a sex-dependent way.

Sex differences in the stress system and addiction vulnerability

One of the leading causes of vulnerability for addiction is prior stress, particularly stress during development, and there are sex differences in how prior stress impacts addiction[132,133]. Furthermore, at multiple levels, the stress system has been shown to interact with addiction in adults in a sex-dependent way, some that are also hormone-dependent[3,132,134,135]. Research is needed on the role of specific estradiol receptor subtypes in sex differences in the effects of stress as it impacts addiction. This brief discussion of the stress system and in sex differences in stress and addiction is included to help highlight the importance of the topic and how it relates to sex differences in vulnerability to addiction.

Gonadal hormones and the hypothalamic-pituitary-adrenal (HPA) axis

The HPA axis is activated in response to a real or perceived threat. This is advantageous in situations where redirection of resources is necessary to increase energy available for survival of an individual[136,137]. On the other hand, chronic stress that results in prolonged activation of the HPA axis, causes a shift in the physiological baseline state and dysregulation of the central nervous system (CNS). Changes to the CNS in response to chronic stress lead to the development of various diseases[138,139].

Neural activation of corticotropin-releasing factor (CRF) release initiates the stress response with HPA axis activation. Secretion of CRF stimulates the anterior pituitary to secrete adrenocorticotropic hormone (ACTH), which stimulates the production and release of glucocorticoids in the adrenal cortex[140,141]. There are sex differences at multiple levels of this signaling cascade such that females have an enhanced response to stress via glucocorticoid production and an enhanced response to negative feedback[142,143].

In addition to its role in the HPA axis, CRF acts centrally by binding to CRF1 and CRF2 receptors in the brain[144,145] to regulate fear, stress and anxiety[146]. There are sex differences in the number and distribution of CRF receptors in the brain, as well as sex differences in CRF trafficking and intracellular signaling mechanisms[147,148]. These mechanistic sex differences are likely driving the sex differences in mood disorders and influences of stress on vulnerability to addiction.

CRF receptors also have direct actions on dopamine transmission in the nucleus accumbens via their location on cholinergic interneurons, which regulate striatal dopamine neurons[149]. Studies in rodents found that psychostimulants, such as cocaine and methamphetamine, produced an even greater increase in brain glucocorticoid levels in females than in males[150,151]. However, the effects of glucocorticoids on dopamine release remains understudied.

In adulthood, gonadal hormones modulate activity of the HPA axis for both sexes. In females, this occurs via estradiol binding at ERα, ERβ and GPER1; in males, testosterone and dihydrotestosterone bind to androgen receptors[152]. Gonadal hormones can also directly affect CRF expression, being that the promotor region of the CRF gene contains gonadal hormone response elements[153,154].

In males, castration decreases overall levels of androgens and results in increased CRF levels and CRF immunoreactivity in the paraventricular nucleus; androgen replacement attenuates this increase[155]. Castration also enhances stress induced corticosterone and ACTH, that can be restored by either testosterone or dihydrotestosterone treatment[156,157].

In females, ovariectomy decreases CRF synthesis in the hypothalamus, although estradiol treatment is not sufficient to restore CRF levels[158]. ACTH and corticosterone levels are also attenuated in ovariectomized females and estradiol does not enhance these levels, presumably because CRF is not restored[152,159].

The functions of estradiol are dependent on actions at specific ER subtypes. For example, treatment with the ERα agonist, propylpyrazoletriol, enhances corticosterone and ACTH levels in the paraventricular nucleus in stressed females[160,161]. Treatment with the ERβ agonist, diarylpropionitrile, has an opposite effect and decreases corticosterone and ACTH in stressed females[161]. From these findings, it appears that ERα and ERβ have antagonistic effects on modulation of HPA axis activation and response to acute stressors in females.

Stress and Sex Differences in Addiction Vulnerability

Stress in humans and animal models affects emotional regulation and has an impact on behaviors such as drug taking[162]. While chronic stress leads to enhanced HPA axis

activation in both men and women, there is a greater incidence of mood-disorders in women[163–165]. The prevalence of drug use in women is reported to relate to coping with psychological disorders, for example, enhanced anxiety sensitivity is associated with greater sedative misuse in women, but not in men[166]. Women, but not men, who meet criterion for psychostimulant dependence report greater psychiatric symptoms than nondependent individuals[167]. This pattern of misuse among mood disorder-prone women is especially troubling as it is not limited by age or drug-type. Together, these reports suggest an interaction between stress and mood-related disorders that is sex-specific.

There are sex differences in vulnerability and resilience to stress throughout the life span[168]. Male offspring (rodents and humans) tend to be at greater risk of experiencing adverse consequences to stress that occurs early in life, during gestation or as infants. Females tend to have compensatory mechanisms that protect them early in life, but are revealed later in life or post-menopause[168]. Nevertheless, both men and women who have experienced childhood sexual and physical abuse have an increased risk for drug use and drug abuse as adults[169,170]. In women, but not men, the intensity of childhood abuse is related to drug abuse relapse[171]. Other studies suggest that each abuse has an independent and additive effect on vulnerability to drug abuse[172]. In adolescence, more stress is linked to an increase in drug abuse liability[173].

In rodents, stress enhances behavioral sensitization, preference for drugs of abuse over other rewards, motivation to attain drugs of abuse and reinstatement of drug-seeking, but the majority of this work has been done in males[174]. After stress, induced by social defeat, both males and females take more cocaine, but females engage in longer cocaine bingeing sessions than males[175].

Social isolation in adult rats enhances motivation for cocaine in females, but not in males[176]. Likewise, females that undergo social isolation during neonatal development show enhanced cocaine self-administration[177]. Stressed females also show greater cue-induced reinstatement for cocaine compared to non-stressed females and stressed or non-stressed males[178]. Finally, the greatest responding to cocaine-paired cues was in stressed females during their proestrous phase, while estradiol levels are high, suggesting an interaction between stress, gonadal hormones, and motivation to attain cocaine[178].

Maternal separation in rodents early in life can increase escalation of drug taking in adulthood, with adult animals who had longer periods of maternal separation consuming more ethanol[179]. After maternal separation, rats showed increased sensitivity to cocaine and stressed-induced sensitization of amphetamine[180]. Males that were isolated postnatally were more sensitive to an acute amphetamine challenge than were females[181,182]. While gestational and early postnatal stress seems to make males more vulnerable to drug sensitivity, prenatal stress affects addictive-like behaviors in both males and females, but in different ways. Prenatal stress that affects drug-taking of the adult offspring, increased the rate of acquisition for males[183], while in a separate study, females showed more addictive-like behaviors (motivation for cocaine, responding in the absence of reinforcement, and responding in the presence of adverse consequences) than males after prenatal stress[184].

Conclusions

Sex differences in the vulnerability for development of substance use disorder has been discussed and the neural mechanisms through which there is enhanced vulnerability in females, as well as greater risk of relapse have been highlighted. In part, this could be because women report taking drugs of abuse as means of coping with psychological disorders, such as depression and anxiety, which may persist during abstinence. Sex differences in the ascending dopamine systems and the regulation of dopamine function by specific ERs has been highlighted as a mechanism mediating sex differences in vulnerability to addiction. The neural adaptations to repeated exposure to psychostimulants are enhanced in females compared to males, which is thought to contribute to greater escalation of drug intake, as well as spontaneous relapse, despite efforts to remain abstinent.

Motivated drug seeking is regulated by the ascending dopamine system which could also be assigning value to drug-related stimuli. Sensitization of the dopamine system, which is greater in females than males, drives an increase in the value of drug-associated cues. Dopamine also has a role in associative learning of reward value and enhancing motivation in males[54]. Other studies that have only used males, suggest that dopamine mediates reward predication error[185,186]. This would be worth exploring in females as well, given that there are sex differences in sensitization, motivation and responsivity to cues.

The role of gonadal hormones in altering drug-seeking behaviors in both sexes is becoming more evident. For example, in females, estradiol potentiates drug-induced dopamine levels in regions of the brain which regulate habitual drug-seeking. Therefore, when estradiol levels are high, females show even greater motivation for drugs of abuse.

Both chronic and acute stress enhance drug seeking in both sexes, but this effect is heightened further in females due to the effect of estradiol on the HPA axis. Prenatal stress effects drug-taking during adulthood in both sexes but via different mechanisms. During adolescence, more sex differences emerge as mood disorders present at a higher rate in females, driving drug taking for self-medication. Once females reach criterion for addiction, they also are more prone to stress-induced relapse than are males. Males also show a greater ability to habituate to stress and may explain why stress is less a risk factor for drug-seeking.

Included throughout this article are areas where research is lacking because only one sex has been included in previous studies. For example, the role of gonadal hormones on drug-seeking in males is understudied. Recent evidence suggests that activation of specific estradiol receptor subtype, GPER-1, may decrease preference for drugs of abuse[72,73]. This evidence supports the idea that while the presence of estradiol may be enhancing drug-abuse in females, it could be decreasing it in males. Understanding the role of gonadal hormones is especially important as we continue to appreciate why women are more vulnerable than males to reward disorders, such as addiction.

One potential target for therapeutic development that is implicated in the discussion of ER subtypes is selective ER agonists and antagonists. A number of drugs have been developed that are selective estrogen receptor modulators (SERMs). The SERMs were developed to target ER-sensitive cancer cells. Many of these SERMs act selectively at one ER in brain

and at different receptors, or not at all in the body. For example, raloxifene and tamoxifen are both SERMS with ERα antagonist activity for breast cancer but with different ER profiles in the brain and other target organs[187–189]. When assessing potential targets in the brain for the pharmaceutical development of addiction treatment drugs, it will be crucial to identify the receptors identity, location, function, and mechanism of action. Of course, caution must be used to determine which action of the SERM is being studied to maximize benefits and minimize side effects.

In conclusion, sex differences in vulnerability to addiction results from developmental exposure to gonadal hormones resulting in sexual differentiation of the brain, combined with experiences during development that interact with the brain and body in different ways. Stress in particular can impact males and females differently during development and as adults to affect vulnerability to addiction. The gonadal hormone estradiol modulates neural activity in areas of the brain at specific target sites to influence dopamine release and motivation for addiction in a sex-specific way. Future research needs to address the mechanisms through which this is happening to identify potential therapeutic sites for treatment of addiction in both men and women.

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Highlights

- Roles of estradiol in sex differences in vulnerability to addiction
- Variable localization and function of ERα, ERß, GPER1 throughout the brain
- Estradiol regulation of dopamine in reward pathway
- Sex differences in stress and vulnerability to addiction
- Gaps in the scientific literature are highlighted throughout

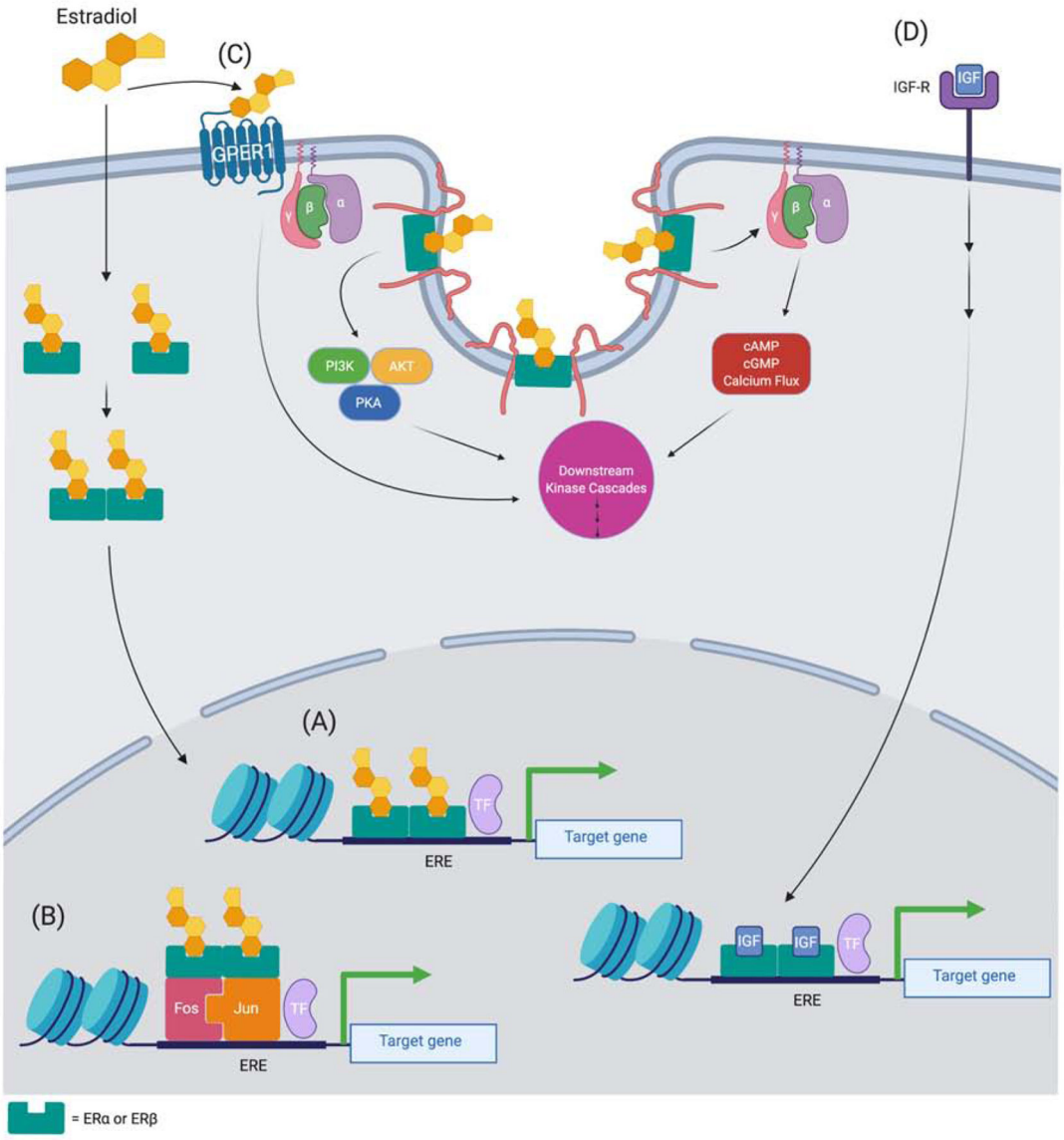

Figure 1.

The four core pathways of estradiol receptor (ER) action include: genomic, tethered, non-genomic, and ligand-independent. (a) The direct most direct mechanism of ER action mediates gene transcription at ERE (estradiol response element) sites. When estradiol (E2) encounters a cell, some will pass through the plasma membrane and into the nucleus. ERs exist as monomers in multiprotein inhibitory complexes until activated by estradiol[197]. This activation causes a conformational change that allows ERs to dimerize and migrate to the EREs[198]. Interaction between this E2/ERs complex, steroid receptor coactivators (SRC), and RNA polymerase II enhances the transcription of downstream targets[199–201]

(b) Activated ERs do not always directly interact with EREs but rather "tether" to transcription factors such as specificity protein (Sp-1) or activating protein-1 (AP-1), to form protein-protein complexes that alter transcription[202203]. In the absence of an activated ER, Sp-1 and AP-1 do not influence transcription[204,205]. (c) Non-genomic actions are

responsible for rapid E2 mediated signaling via extranuclear ERs bound to different membranes in the cell[206]. Caveolae are populated by g-protein subunits and upon activation, these proteins cause signaling cascades that ultimately produce cAMP, cGMP, calcium flux, and protein-kinase activation[78,207,208]. There are four major protein-kinase cascades: phospholipase C (PLC)/protein kinase C (PKCs), Ras/Raf/MAPK, phosphatidyl inositol 3 kinase (PI3K)/AKT, and cAMP/ protein kinase A (PKA)[78]. GPER-1 is a unique ER in the sense that it can initiate these signaling cascades on its own. (d) Ligand-independent mechanisms work in the absence of E2. Upon activation, growth factor receptors (GFRs) on the plasma membrane initiate signaling cascades, as described above[209]. This results in the activation of nuclear ERs by either phosphorylating the receptor itself or stimulating the recruitment of steroid receptor coactivators (SRCs).
Adapted from Yoest et al, 2018[120]

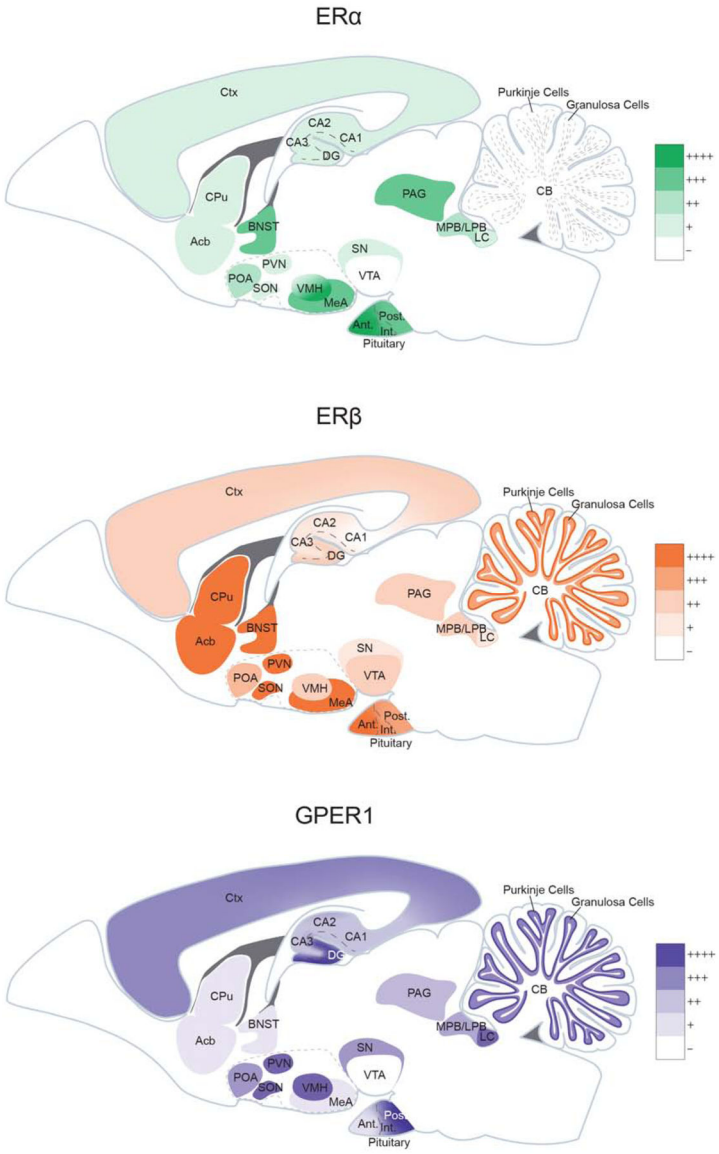

Figure 2.

Graphical representation ERα, ERβ, and GPER1 localization in the CNS, as described in Table I; higher color saturation indicates higher signal intensity.

Abbreviations: PFC, prefrontal cortex; F, frontal lobe; P, parietal lobe; T, temporal lobe; O, occipital lobe; DG, dentate gyrus; BNST, bed nucleus of the stria terminalis; PVN, paraventricular nucleus of the hypothalamus; SON, supraoptic nucleus of the hypothalamus; VTA, ventral tegmental area.

Table I.

Distribution of estradiol receptors and corresponding mRNA transcript in the CNS of mice (red) and rats (black).

			ERα		ERβ		GPER1	
			mRNA	Protein	mRNA	Protein	mRNA	Protein
Cerebral Cortex (PFC;F, P, T, O)		F	–[138]	+[139]	+[138]	[x],++,++,++,++[145]	+++[276]	[x]; +++[149]
		M	–[138]		+[138]		+++[276]	[x]; +++[149]
Hippocampus (CA1, CA2, CA3, DG)		F	+, +, ++, [x][138]	+,+,+,+[139]	+,–,+,[x][138]	–, +, +, ++[145]	++[276]	++,++,++,++++[149]
		M	+, +, ++, [x][138]		+,–,+,[x][138]		++[276]	++,++,++,++++[149]
Striatum		F		+[139]		++++[145]*		+(f)[149]
		M						+(f)[149]
BNST		F	++++[137]; ++[138]*	+++[139]	++++[137]; +[138]*	++++[145]*		+[149]
		M	++[138]*		+[138]*			+[149]
Hypothalamus	PVN, SON	F	–, –[137]	+,+[139]	+, +++[137]	++++[145]		++++,++++[149]
		M						++++,++++[149]
	Preoptic Area (Medial, Lateral, Periventricular)	F	++++, ++, +++[137]; ++++, ++, ++[138]	+++,+,++[139]	++++, ++, +++[137]; +++,–,++[138]	++, ++, +++[145]		+++,+,+++[149]
		M	++++, ++, ++[138]		+++,–,++[138]			+++,+,+++[149]
	Ventromedial Hypothalamus (Dorsomedial., Ventrolateral)	F	++, ++++[138]	+, ++++[139]	–, ++[138]	++[145]		++++,++++[149]
		M	++, ++++[138]		–, ++[138]			++++,++++[149]
Medial Amygdala		F	++++[137]; ++[138]	+++[139]	+++[137]; ++[138]	++++[145]		+[149]
		M	+++[138]		++[138]			+[149]
VTA		F	+[137]	–[139]	++[137]	++[145]		–[149]
		M						–[149]
Periaqueductal Grey		F	+[137], +++[138]	+++[139]	+[137]; +[138]	++[145]		++[149]
		M	+++[138]		+[138]			++[149]
Substantia Nigra		F	++[138]	+[139]	+[138]	+[145]		+++[149]
		M	++[138]		+[138]			+++[149]
Locus Coeruleus		F	+[137]; +++[138]	+[139]	+[137]; –[138]	+[145]		++++[149]
		M	+++[138]		–[138]			++++[149]
Parabrachial (Medial, Lateral)		F	–, +[137]	+,++[139]	+,+[137]	++,++[145]		–,+++[149]
		M						–,+++[149]
Cerebellum (purkinje cells, granulosa cells)		F	–[138]	–[139]	++[138]	+, +++[145]		++++[149]
		M	–[138]		++[138]			++++[149]
Pituitary Gland (Ante., Post., Int.)		F		++++, [x], +++[140]		++++, [x], +++[140]	+, –[149]	+, ++++(f), +++[149]
		M					+, –[149]	+, ++++(f), +++[149]

Data have been normalized to fit the following scale[121]: –, no signal; +, low signal; ++, moderate signal; +++, intense signal; ++++, very intense signal. Comma separations correspond to respective subregions; when no commas are used, the whole region is implicated; [x] indicates a subregion not specifically noted by the source's data.

Abbreviations: PFC, prefrontal cortex; F, frontal lobe; P, parietal lobe; T, temporal lobe; O, occipital lobe; DG, dentate gyrus; BNST, bed nucleus of the stria terminalis; PVN, paraventricular nucleus of the hypothalamus; SON, supraoptic nucleus of the hypothalamus; VTA, ventral tegmental area.