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Behavioral Sex Differences in Cocaine and Opioid Use Disorders: The Role of Gonadal Hormones.

Melissa C. Knouse[1], **Lisa A. Briand**[1,2]

[1]Department of Psychology, Temple University

[2]Neuroscience Program, Temple University

Abstract

Females are more vulnerable than males to many aspects of cocaine use disorder. This vulnerability also translates to opioid use disorder, with females exhibiting stronger behavioral responses than males to drugs such as heroin and morphine. While there is evidence for many overlapping neural mechanisms underlying cocaine and opioid abuse, there is also a breadth of evidence indicating divergent effects of the drugs on synaptic plasticity. This makes it unclear whether the behavioral sex differences seen in substance use disorder across different drugs of abuse rely on the same mechanisms. Ovarian hormones have consistently been implicated as drivers of the behavioral sex differences in cocaine taking and seeking. While there are far fewer studies on the role of ovarian hormones in opioid use disorder, the existing data suggest that ovarian hormones may not drive these behavioral effects in the same manner as in cocaine use disorder. This review highlights evidence that behavioral sex differences in substance use disorder might be driven by different mechanisms depending on drug class.

Keywords

substance use disorder; estradiol; testosterone; sex differences; opioids; cocaine

Introduction

Substance use disorder (SUD) is a growing public health crisis in the United States, with overdose deaths steadily increasing through 1999–2018 (Hedegaard et al., 2020). While the ongoing opioid epidemic is a large driver of this, overdose deaths involving cocaine are also rising. Rates of ageadjusted overdose deaths involving synthetic opioids other than methadone increased by 10% from 2017–2018 and overdose deaths involving cocaine more than tripled from 2012–2018 (Hedegaard et al., 2020). While there are FDA-approved pharmacotherapies to treat opioid use disorder, many of them are limited in efficacy and none are currently approved to treat cocaine use disorder. Furthermore, the available

Address correspondence to: Lisa A. Briand, Ph.D. Temple University, Department of Psychology Weiss Hall 1701 North 13th Street, Philadelphia, PA 19122, Tel: (215) 204-7311, lbriand@temple.edu.

pharmacotherapies for opioid use disorder do not yield the same treatment outcomes in males and females. After 2 weeks of treatment with buprenorphine, a larger percentage of males remain abstinent from illicit opioids than females (Johnson et al., 1995). This eventually reverses, however, and more females remain abstinent from illicit opioids than males at 17 and 24 weeks of treatment (Jones et al., 2005; Schottenfeld et al., 1998). This is possibly due to sex differences in the development and experience of substance use disorder. The information on opioid use disorder is less extensive, though existing research shows that males and females also do not develop and experience opioid use disorder in the same manner. Across the board, it appears that females are more vulnerable than males to cocaine and opioid use disorders.

While the behavioral sex differences in opioid and cocaine use disorder overlap, the neural mechanisms underlying these differences are less understood. Cocaine and opioids produce their rewarding effects through similar mechanisms, though their effects on the brain diverge in numerous ways. This makes it difficult to determine whether behavioral sex differences in SUD develop through the same mechanisms for different drugs of abuse. While various mechanisms have been implicated, ovarian hormones are likely the primary driver of the behavioral sex differences seen in cocaine use disorder. It is unclear, however, whether ovarian hormones also drive the behavioral sex differences seen in opioid use disorder. It seems plausible, given that cocaine and opioids have many overlapping effects on the brain. The opioid literature is limited, however, and paints a slightly different story. Overall, it seems overlapping behavioral sex differences in drug abuse might not be driven by the same biological mechanisms. This review highlights the need for further exploration of the mechanisms underlying sex differences in opioid use disorder.

Behavioral sex differences in substance use disorder

Both preclinical and clinical research have traditionally ignored sex as a biological variable. The majority of research was conducted in males, leading to heavily biased results (Greenfield et al., 2007). Unfortunately, male biases in biomedical research have led to economic loss and unintended fatalities (Lee, 2018).These consequences led to NIH mandates for the inclusion of female subjects in research, which has exponentially increased the number of published reports about substance abuse in women (Greenfield et al., 2007). As substance abuse research involving female subjects increases, new trends are emerging.

According to the 2018 National Survey on Drug Use and Health, the rate of illicit drug use other than marijuana in those aged 12+ is higher in males than in females (SAMHSA, 2018). However, this gap is steadily closing, likely due to attitude changes towards women in the home and workplace (Brady and Randall, 1999). Despite the fact that the rate of abuse and dependence is currently higher in males, females are more vulnerable to many aspects of SUD. While the breadth of research on sex differences in cocaine abuse is extensive, less is known about sex differences in opioid abuse. However, with the ongoing opioid epidemic, new research has indicated that opioids likely have similar effects in females as cocaine. Both lines of research point to the same trend: females are more vulnerable than males to many aspects of cocaine and opioid use disorders.

Clinical research indicates that women are more sensitive to many aspects of cocaine use and abuse. Women report higher cocaine craving following exposure to drug-related cues, more frequently having used more cocaine than they meant to, and more frequently having used despite trying not to than men (Kennedy et al., 2013). Women also report a higher desire to use cocaine, lower desires to not use cocaine, and lesser highs than men (Elman et al., 2001; Sofuoglu et al., 1999). Together, these data indicate that men and women do not experience cocaine use disorder in the same way. Biological sex therefore appears to influence responses to cocaine, likely increasing female vulnerability to cocaine use disorder.

Preclinical work generally recapitulates the clinical findings, with female rodents exhibiting increased behavioral responses to cocaine. It is important to note that these differences are not always seen and the effect of sex in preclinical models of substance use disorder often depends on paradigm (Larson et al., 2005). Nonetheless, a breadth of studies indicate that female rodents acquire cocaine self-administration more rapidly, self-administer more cocaine, and exhibit higher responding during reinstatement and on progressive ratio (PR) schedules than males (Bechard et al., 2018; Carroll et al., 2002; Festa and Quinones-Jenab, 2004; Kerstetter et al., 2008; Lynch and Carroll, 2000; Lynch and Taylor, 2004; Ramoa et al., 2013; Roberts et al., 1989) Additionally, females are more sensitive to factors that contribute to the escalation of cocaine-taking and they acquire cocaine conditioned place preference quicker and at lower doses than males (Roth and Carroll, 2004; Russo et al., 2003). These differences are present from an early age, as adolescent females also acquire self-administration more readily and respond at higher levels in a PR paradigm than males (Lynch, 2008). Together, these data indicate that females are more vulnerable than males to the behavioral effects of cocaine. Preclinical models of cocaine taking, seeking, and relapse indicate that cocaine interacts with biological sex in some manner to alter addiction-like behaviors.

These effects do not appear to be specific to cocaine, as the emerging opioid literature also indicates that females are more susceptible to the addiction-like effects of opioids. Clinically, women report higher baseline opioid craving and higher heroin craving following exposure to drug-paired cues than men (Back et al., 2011; Yu et al., 2007). Preclinically, females acquire heroin self-administration more rapidly and take more heroin, fentanyl, oxycodone, and morphine than males (Carroll et al., 2002; Cicero et al., 2003; Kimbrough et al., 2020; Klein et al., 1997; Lynch and Carroll, 1999; Zanni et al., 2020). Additionally, females respond more than males during cue-induced heroin reinstatement and for morphine on a PR schedule (Cicero et al., 2003; Vazquez et al., 2020). Females also exhibit higher morphine withdrawal scores compared to males (Reiss et al., 2020).

Given these findings, it seems the existing literature on sex differences in opioid abuse points to a similar trend: females are more susceptible to many aspects of opioid use disorder. The available pharmacotherapies to treat opioid use disorder are unfortunately limited by side effects and efficacy. Through understanding how sex influences SUD, we might be able to create more targeted pharmacotherapies that would limit side effects and increase efficacy. While the behavioral sex differences in opioid and cocaine use disorders seem to overlap, it is unclear whether they are driven by the same mechanisms.

The influence of gonadal hormones on behavior

Biological sex can influence behavior via actions of the different complement of genes on sex chromosomes and via circulating gonadal hormones (Arnold, 2009). Gonadal hormones are capable of modulating behavior in two ways: through organizational and activational effects. The organizational-activational hypothesis of gonadal hormones was first proposed by Phoenix and colleagues (Phoenix et al., 1959). Organizational effects of hormones permanently shape the brain. These effects can occur throughout life during critical periods such as puberty (Romeo, 2003). A crucial time point for the organizational effects of hormones is around the time of birth. During the perinatal period, testosterone masculinizes the male brain (Phoenix et al., 1959). Importantly, perinatal masculinization alters excitatory synaptic input in the nucleus accumbens (Cao et al., 2016). Therefore, it is possible that organizational effects of gonadal hormones during the perinatal period shape the brain in a way that primes females to be more vulnerable to SUD than males. Activational effects of hormones are transient, due to circulating levels of gonadal hormones, and usually reversible. The activational effects of gonadal hormones occur when they interact with the masculinized or feminized brain to influence behavior. Once onboard, drugs of abuse can interact with circulating ovarian hormones in a manner that makes females more susceptible than males to subsequent use (Baker et al., 2003; Becker and Hu, 2008; Festa and Quinones-Jenab, 2004; Jackson et al., 2006; Perry et al., 2013). Understanding the role of both organizational and activational effects of gonadal hormones on reward signaling and the response to drugs of abuse could provide us with insight into mechanisms underlying behavioral sex differences. It is possible that the masculinization (or lack thereof) of the brain affects vulnerability to drug use in adulthood. Furthermore, interactions amongst circulating gonadal hormones and drugs of abuse also likely influence how males and females respond in the context of SUD. Understanding how gonadal hormones might affect vulnerability to SUD will ideally lead to better treatment plans and subsequent outcomes.

Gonadal hormones and substance abuse

Cocaine—It is well-established that ovarian hormones play a key role in sex differences in cocaine abuse. The human menstrual cycle lasts approximately 28 days and is divided into luteal and follicular phases. Estrogen levels peak about halfway through the cycle, followed by a peak in progesterone (Staley and Scharfman, 2005). In rodents, the estrus cycle lasts approximately 4 days and is divided into 4 stages: proestrus, estrus, metestrus, and diestrus. Estrogen levels peak during proestrus and progesterone levels peak in between proestrus and estrus (Staley and Scharfman, 2005). Changes in ovarian hormone levels throughout both the human and rodent menstrual and estrus cycles are known to influence substance use behaviors, as circulating estradiol levels significantly contribute to the enhanced sensitivity to the reinforcing effects of cocaine seen in females (Lynch, 2008). Clinically, the subjective effects of cocaine vary throughout the menstrual cycle (Evans and Foltin, 2010; Sofuoglu et al., 1999; Terner and de Wit, 2006). Preclinically, female rats in estrus exhibit higher breakpoints in a PR paradigm but remain stable in males (Lacy et al., 2016; Roberts et al., 1989). Additionally, female rats in estrus exhibit greater responding during self-administration, extinction, and reinstatement than either males or non-estrus females (Feltenstein et al., 2009; Feltenstein and See, 2007; Kippin et al., 2005; Lynch, 2008).

Together, these data indicate the reinforcing efficacy of cocaine is dramatically altered by fluctuating levels of ovarian hormones throughout the estrus cycle.

Further confirming this association, studies ovariectomizing (OVX) female rats have shown that ovarian hormones increase vulnerability to cocaine abuse. Blocking the activational effects of ovarian hormones via OVX in adulthood affects behavioral responses to cocaine (Russo et al., 2003; Sircar and Kim, 1999; Walker et al., 2001). OVX decreases the magnitude of cocaine conditioned place preference, the magnitude of reinstatement, and the percentage of animals acquiring self-administration (Larson et al., 2005; Lynch et al., 2001; Russo et al., 2003). Furthermore, estradiol replacement to OVX females facilitates cocaine self-administration and conditioned place preference (Hu et al., 2004; Perry et al., 2013; Ramoa et al., 2013; Segarra et al., 2010; Twining et al., 2013). This effect is specific to females, as a dose of estradiol that enhances self-administration in OVX females has no effect on behavior in castrated males (Jackson et al., 2006). Estradiol replacement also increases cocaine reinstatement and breakpoints on a PR schedule (Becker and Hu, 2008; Doncheck et al., 2018; Larson and Carroll, 2007; Larson et al., 2005; Perry et al., 2013). Thus, removal of ovarian hormones seems to decrease behavioral responses to cocaine in female rats, while hormonal replacement facilitates addiction-like behaviors. However, there are multiple studies that demonstrate differing effects of sex and gonadal hormones on behavioral responses to cocaine.

While some studies show differences in cocaine progressive ratio breakpoint throughout the menstrual cycle (Mello et al., 2007), other studies do not (Cooper et al., 2013). Furthermore, sex and gonadal hormone status do not always influence cocaine self-administration in cynomolgus monkeys or rats (Baptista et al., 2004; Kerstetter et al., 2012; Mello et al., 2007). There are many possibilities for these discrepancies in the literature. Methodological differences are a likely explanation, as increases in progressive ratio during estrus in cynomolgus monkeys are seen at a low dose of cocaine (Mello et al., 2007). Furthermore, the paradigm utilized influences the effect of estrus on cocaine-seeking (Kerstetter et al., 2008). It is proposed that duration of cocaine exposure influences estrogen levels and duration of estradiol replacement can modulate dopamine release in the striatum (Becker, 1990; Larson et al., 2005; Lynch and Taylor, 2005). This indicates that the paradigm used in estradiol replacement studies could significantly impact behavioral responses to cocaine. Indeed, the length of estradiol replacement significantly alters cocaine reinstatement and the dose of cocaine used significantly modulates the effect of estradiol replacement on cocaine conditioned place preference scores (Bobzean et al., 2014; Larson et al., 2005).

Overall, the literature indicates a strong, but nuanced, role of ovarian hormones in cocaine abuse. Factors such as reinforcement schedule, dose, and prior behavioral experience are frequent explanations for discrepancies in this literature. However, there is a significant role of progesterone in behavioral responses to cocaine that is often ignored. Clinically, progesterone attenuates the “good drug effect” of smoked cocaine in women and decreases cocaine use in post-partum women (Evans and Foltin, 2010; Yonkers et al., 2014). Preclinically, progesterone decreases cocaine self-administration in non-human primates and decreases escalation of cocaine taking in rodents (Larson and Carroll, 2007; Mello et al., 2011). Furthermore, cocaine seeking is at its lowest when progesterone is at its highest, and

cocaine seeking is at its highest when progesterone levels are at their lowest (Feltenstein and See, 2007). These studies exemplify the need for further consideration of progesterone in the behavioral sex differences seen in cocaine abuse. While there is a demonstrated role for estrogen in these differences, progesterone has a consistent effect on dampening behavioral responses to cocaine in females.

Less is known about the perinatal organizational effects of gonadal hormones on cocaine abuse, as prepubertal animals are less commonly studied. While female rats exhibit higher cocaine-induced locomotor activity than males in adulthood, there do not appear to be sex differences in this measure in prepubertal rats (Cailhol and Mormede, 1999; Kuhn et al., 2001; Segarra et al., 2010; Ujike et al., 1995). However, prepubertal gonadectomy has opposing effects on locomotor activity in males and females. Male rats gonadectomized prepubertally exhibit increased behavioral responsiveness to cocaine while female rats gonadectomized prepubertally exhibit decreased behavioral responsiveness to cocaine (Parylak et al., 2008). This suggests that there are multiple organizational and activational effects of gonadal hormones that modulate responsiveness to cocaine. Furthermore, it also demonstrates that male gonadal hormones might be protective against some aspects of SUD, while female gonadal hormones increase vulnerability to SUD.

Testosterone appears to play a smaller, but still significant, role in the sex differences seen in cocaine use. Testosterone replacement to castrated male rats reduces cocaine-induced focused stereotypy sensitization and partially restores cocaine-induced reductions of dopamine uptake in the striatum, indicating that testosterone modulates cocaine-induced alterations of dopamine homeostasis (Chen et al., 2003). Furthermore, intact male rats display sensitization to cocaine-induced stereotypic activity over the course of a week while castrated male rats display sensitization only following a cocaine challenge (Chin et al., 2002). This shows that behavioral stereotypy can sensitize to cocaine without testosterone, albeit in a different manner. It is plausible that testicular hormones are protective against cocaine abuse, whereas ovarian hormones are detrimental to cocaine abuse.

Overall, there is a breadth of evidence indicating that gonadal hormones modulate behavioral responses to cocaine. Both clinical and preclinical literature indicate that ovarian hormones are a major driver of female vulnerability to cocaine use and abuse. Removal of ovarian hormones blocks behavioral responses to cocaine and estradiol replacement rescues these effects. What is unknown, however, is whether gonadal hormones are also the predominant driver of behavioral sex differences in opioid abuse.

Opioids—Unfortunately, the work examining the effects of gonadal hormones on opioid abuse is limited. Clinically, little is known about subjective responses to opioids throughout the menstrual cycle in patients with SUD. While some pain literature indicates the analgesic efficacy of opioids may vary throughout the human menstrual cycle, the results are conflicting (Ribeiro-Dasilva et al., 2011; Terner and de Wit, 2006). While there are gaps in the clinical literature, there are behavioral differences seen in preclinical models of opioid use disorder throughout the estrus cycle. Female rats take a similar number of heroin infusions during estrus, metestrus, and diestrus but self-administer significantly less during

proestrus (Lacy et al., 2016). Together, these data highlight the possibility that opioid use disorder is similarly influenced by ovarian hormones as cocaine.

Just as with cocaine, behavioral responses to opioids can vary following OVX. OVX in female mice decreases the magnitude of morphine conditioned place preference similarly to cocaine, an effect that can be reversed with estradiol replacement (Mirbaha et al., 2009). Additionally, estradiol replacement following OVX in rats increases acquisition of heroin self-administration and infusions during the last 5 days of acquisition compared to OVX conspecifics treated with vehicle (Roth et al., 2002). Preclinical pain literature indicates an organizational effect of perinatal gonadal hormones on opioid-induced analgesia, as gonadectomy shortly after birth, but not in adulthood, significantly alters morphine analgesia in both male and female rats (Borzan and Fuchs, 2006; Cataldo et al., 2005; Cicero et al., 2002; Krzanowska et al., 2002). These results indicate significant organizational and activational effects of gonadal hormones in responses to opioids. While this literature would lead to the conclusion that gonadal hormones drive cocaine and opioid use disorders similarly, many studies have found opposing results.

For example, OVX followed by estradiol replacement in rats has no effect on heroin self-administration and responding on a PR schedule (Stewart et al., 1996). Furthering this, multiple studies have found no effect of OVX at all in rat models of opioid use disorder. OVX has no effect on heroin self-administration, seeking, or responding on a PR schedule (Sedki et al., 2015; Stewart et al., 1996). Additionally, while estradiol replacement to OVX animals increases the number of heroin infusions earned, sham controls do not differ from OVX controls (Roth et al., 2002). This makes the role of ovarian hormones in opioid use disorder difficult to understand, as blocking circulating ovarian hormones in rats does not always affect taking and seeking behavior on its own. This calls into question whether the activational effects of ovarian hormones play the same role in cocaine and opioid abuse.

Adding to the confusion, OVX in mice actually increases conditioned place preference at a dose of 10 mg/kg morphine, an effect that is then decreased by estradiol replacement (Mirbaha et al., 2009). Additionally, estradiol replacement blocks increased heroin seeking seen in OVX female rats following food restriction (Sedki et al., 2015). However, it should be noted that this effect may be mediated, in part, by the anorexic properties of estradiol (Sedki et al., 2015). While the role of progesterone in opioid abuse is largely unknown, there is evidence it does not affect motivation for heroin in rats (Stewart et al., 1996). Thus, while the role of ovarian hormones in cocaine taking and seeking is well-established, the role in opioid taking and seeking is not. Ovarian hormones have been shown to promote, block, or not affect the behavioral effects of opioids, making it difficult to understand their role in these behaviors. This leads to the possibility that ovarian hormones do not play the same role in the sex differences seen in cocaine an opioid abuse.

Although there is little work examining the role of testosterone in opioid use disorder, there is evidence that testosterone and opioids interact. Both morphine and heroin reduce testosterone levels in rats and humans, indicating some form of interaction between them (Cicero et al., 1976; Mendelson and Mello, 1975; Yilmaz et al., 1999). The majority of the literature on this topic focuses on how testosterone modulates opioid antinociception.

Female and castrated male rats develop morphine tolerance slower than intact male or testosterone-treated female rats (South et al., 2001). Additionally, naloxone can increase pain threshold and enhance morphine-induced analgesia in castrated rats. This can be abolished with testosterone treatment (Rao and Saifi, 1985). There appears to be a strong organizational effect of neonatal testosterone on morphine antinociception, as males gonadectomized neonatally exhibit reduced morphine analgesia in adulthood and female rats treated neonatally with testosterone exhibit increased morphine analgesia (Borzan and Fuchs, 2006; Cataldo et al., 2005; Cicero et al., 2002; Krzanowska et al., 2002). Overall, this indicates there are organizational and activational effects of testosterone that alter the analgesic efficacy of opioids. This provides evidence that testosterone might also modulate behavioral responses in opioid use disorder.

The role of circulating gonadal hormones in opioid use disorder remains unclear. While ovarian hormones exhibit clear organizational and activational effects in cocaine abuse, there are inconsistent results in opioid abuse. OVX blunts behavioral effects of cocaine, an effect that can be reversed with estradiol replacement. However, OVX does not consistently affect behavioral effects of opioids. Furthermore, estradiol replacement can decrease, increase, or not affect these responses. These studies indicate that the role of the activational and organizational effects of ovarian hormones in SUD might differ by drug class (see table 1). It is possible that there are activational effects of ovarian hormones that are not the same following cocaine or opioid exposure. The role of testosterone in SUD is less clear. It appears that testosterone may be protective against SUD, but a lack of data prevents any definitive conclusions. Overall, it seems that ovarian hormones might not play the same role in opioid use disorder as they do in cocaine use disorder. Behavioral sex differences themselves might be similar across drug classes, but the underlying mechanisms might not. Given the lack of available studies, further research examining how gonadal hormones and opioids interact are crucial to understand behavioral sex differences in opioid use disorder.

Neural mechanisms underlying the reinforcing properties of cocaine and opioids

Given the existing literature on gonadal hormones and substance use disorder, it seems behavioral sex differences in cocaine and opioid abuse might be driven by different mechanisms. This seems in direct contradiction to the fact that cocaine and opioids both produce their rewarding effects through activation of the mesolimbic dopamine system. Put simply, both drugs increase dopamine release from the ventral tegmental area (VTA) to the nucleus accumbens (NAc), albeit through slightly different mechanisms. Cocaine, a dopamine, serotonin, and norepinephrine transporter blocker, prevents neurotransmitter clearance from the synapse. Blocking the dopamine transporter (DAT) results in a flood of dopamine in the NAc, producing the rewarding effects of the drug (Hummel and Unterwald, 2002). Opioids primarily bind to μ opioid receptors on GABAergic neurons in the VTA, leading to disinhibition of dopamine projections to the NAc. Overall, this induces an increase in dopaminergic signaling to the NAc (Fields and Margolis, 2015). While they work through slightly different mechanisms, the end result is a flood of dopamine in the NAc which produces the rewarding effects of drug use.

The mechanisms driving relapse to opioids and cocaine overlap as well. Specifically, it has been proposed that the glutamatergic effects of the drugs overlap (Hearing et al., 2018). In basal conditions, the cystine-glutamate antiporter (system xc-) increases extracellular glutamate levels which in turn stimulates presynaptic group II metabotropic glutamate receptors (mGluR2/3), resulting in a decrease of excitatory transmission (Moran et al., 2005). Both opioids and cocaine disrupt glutamate homeostasis during withdrawal. This is in part due to decreased function of system xc- and mGluR2/3 (Bossert et al., 2006; Knackstedt et al., 2010a; Xi et al., 2002; Zhou and Kalivas, 2008). Restoring function to system xc-, usually by administration of N-acetylcysteine, reverses cocaine-mediated alterations of long-term potentiation (LTP) and long-term depression (LTD), prevents both cue- and drug-primed cocaine and heroin reinstatement, and induces a lasting reduction in cue- and heroin-induced seeking (Baker et al., 2003; Kau et al., 2008; Madayag et al., 2007; Moussawi et al., 2009; Moussawi et al., 2011; Zhou and Kalivas, 2008). This effect appears to be at least partially dependent on mGluR2/3, as antagonists block the ability of N-acetylcysteine to restore LTP following cocaine self-administration (Moussawi et al., 2009). Additionally, cocaine conditioned reinstatement, cocaine-primed reinstatement, and context-induced heroin seeking can be attenuated with mGluR2/3 agonists (Baptista et al., 2004; Bossert et al., 2006; Peters and Kalivas, 2006). This indicates that both cocaine and opioid exposure produce alterations to system xc- and mGluR2/3 in the NAc that disrupt glutamate homeostasis and set the stage for relapse.

Overall, the literature points to common mechanisms underlying cocaine and opioid relapse: altered glutamate homeostasis in the NAc via decreased function of system xc- and mGluR2/3. The mechanistic overlap seen in cocaine and opioid use disorders leads to the hypothesis that similar mechanisms might actually drive female vulnerability to both opioid and cocaine abuse. Unfortunately, the issue is not so clear cut. While there are overlapping mechanisms underlying cocaine and opioid abuse, there is strong evidence indicating that cocaine and opioids have differing effects on synaptic plasticity.

LTP and LTD are two forms of synaptic plasticity that can be altered by exposure to drugs of abuse. Cocaine consistently disrupts LTD in the NAc. A single exposure can abolish LTD (Fourgeaud et al., 2004) and various models of chronic exposure and withdrawal can induce persistent inhibition of LTD in the core and shell regions (Knackstedt et al., 2010a; Martin et al., 2006; Moussawi et al., 2009; Thomas et al., 2001). This impairment is likely due to downregulated mGluR5 and subsequently disrupted system xc- function (Fourgeaud et al., 2004; Knackstedt et al., 2010a; Moussawi et al., 2009). N-acetylcysteine administration restores the deficits, an effect that is dependent on mGluR5 but not mGluR2/3 (Moussawi et al., 2009). Impairment also appears to depend on subregion, as it persists in the core region during abstinence but does not persist in the shell (Martin et al., 2006).

Opioids also exert long-lasting impairments in LTD in the NAc. Prolonged withdrawal from opioids impairs LTD in both the NAc core and shell (Dong et al., 2007; Qian et al., 2019; Shen and Kalivas, 2013). Interestingly, this effect appears to be due to downregulation of mGlur2/3 (Dong et al., 2007; Robbe et al., 2002). This is inconsistent with the prior results showing cocaine-mediated disruptions in LTD are due to mGluR5, not mGluR2/3. This leads to the possibility that while the net results are similar, different mechanisms might

drive the impaired LTD seen in the NAc following cocaine and opioid exposure. Furthering this, there are also differences seen in synaptic potentiation following drug exposure.

Chronic cocaine, regardless of whether it is followed by extinction, induces a LTP-like state in the NAc. Frequently, this state prevents the induction of further LTP (Moussawi et al., 2009). Thus, many studies show that cocaine actually prevents the induction of LTP in the NAc (Knackstedt et al., 2010b; Moussawi et al., 2009). Similarly, acute morphine withdrawal impairs induction of LTP in the NAc shell, an effect that is restored over prolonged withdrawal (Dong et al., 2007). Within the NAc core, heroin self-administration followed by extinction also impairs induction of LTP (Shen and Kalivas, 2013). While this leads to the possibility that cocaine and opioids exert similar effects on synaptic plasticity, the NAc actually exhibits a LTD-like state during heroin withdrawal (Shen et al., 2011). There is a decrease in the AMPA/NMDA ratio in the NAc core during heroin extinction which is due to increases in NR2B and NMDA current decay time (Shen et al., 2011). Overall, this indicates the NAc core is likely in a depotentiated state following heroin exposure. Therefore, it appears that while both opioids and cocaine can impair LTP induction, they lead to opposing states in the NAc.

Overall, this indicates there are opposing changes to synaptic plasticity in the NAc following cocaine and opioid exposure (Shen and Kalivas, 2013). This can lead to similar outcomes such as blunted LTD and difficulty inducing LTP even though the underlying mechanisms are not the same. Synaptic plasticity is an important modulator of SUD (Kauer and Malenka, 2007), therefore changes in synaptic plasticity can drive behavioral responses to drugs of abuse. These differences in synaptic plasticity within the NAc represent the possibility that different mechanisms might drive the overlapping behavioral sex differences in SUD.

Differences in synaptic plasticity following exposure to drugs of abuse can also be examined using dendritic spine density. Changes to spine density in the NAc core are thought to promote cocaine craving over time (Christian et al., 2017). Interestingly, different classes of drugs alter spine density in different ways. Specifically, cocaine and opioids have opposing effects on spine density within the mesolimbic dopamine system. Cocaine self-administration increases dendritic branching and density of dendritic spines in NAc shell medium spiny neurons and prefrontal and parietal pyramidal cells (Robinson et al., 2001). Repeated cocaine increases spine density in the shell (Dumitriu et al., 2012) and core (Norrholm et al., 2003). Interestingly, the effect of cocaine on spine density in the core appears to be time-dependent, with density actually decreasing at certain time points following exposure (Dumitriu et al., 2012; Siemsen et al., 2019). Nonetheless, cocaine overall induces increases in spine density in the NAc. This is interesting, as the opposite effect is generally seen following opioid exposure.

Both self-administered and experimenter-administered morphine decrease dendritic spine density in the NAc shell (Robinson et al., 2002). Along these lines, repeated morphine exposure followed by a withdrawal paradigm decreases dendritic spine density on MSNs in the NAc shell (Diana et al., 2006; Kasture et al., 2009; Robinson and Kolb, 1999; Spiga et al., 2005), core (Leite-Morris et al., 2014), and on prefrontal pyramidal cells (Robinson and Kolb, 1999). Together, these data indicate that opioids decrease dendritic spine density

within the NAc. As cocaine generally does the opposite, it seems the behavioral outcomes in opioid and cocaine use disorders might be driven by different mechanisms.

Taken together, these studies indicate that opioids and cocaine might have functionally distinct effects on synaptic plasticity. Both drugs are capable of blunting LTD and impairing LTP in the NAc, which alludes to overlapping effects on synaptic plasticity. However, cocaine induces a LTP-like state in the NAc whereas opioids induce a LTD-like state. Furthermore, cocaine increases dendritic spine density in the NAc. Opioids, however, most often decrease spine density within the NAc. Opposing alterations of synaptic and structural plasticity in the NAc indicate that opioids and cocaine might not drive SUD in the same manner. This information makes it unclear whether the overlapping behavioral sex differences seen in opioid and cocaine abuse stem from the same neural mechanisms. The interactions between biological sex and drugs of abuse could differ by drug class, even though they lead to similar behavioral outcomes.

Effects of gonadal hormones on dendritic spine density

In addition to drugs of abuse, gonadal hormones also modulate spine density in the brain. It is possible drugs of abuse interact with gonadal hormones to modulate synaptic plasticity. While the behavioral outcomes of these interactions may be similar, different drugs of abuse might interact with gonadal hormones to modulate synaptic plasticity in different manners. The predominant portion of studies investigating gonadal hormones and spine density examine their effects on hippocampal circuits involved in learning and memory. These studies give us a glimpse into how gonadal hormones can differentially affect synaptic plasticity in the brain, which might be a mechanism that makes females more vulnerable to the effects of drugs of abuse.

Within the hippocampus, dendritic spine density fluctuates throughout the estrus cycle in females with the lowest density seen during the estrus phase (Brusco et al., 2008). OVX decreases spine density in pyramidal CA1 neurons in the hippocampus (Wallace et al., 2006). Estradiol administration increases CA1 apical spine density, but 10 weeks following OVX the ability of estradiol to increase CA1 apical spine density is decreased. In contrast, a different protocol of estradiol administration failed to alter apical spine density and actually decreased basal spine density (McLaughlin et al., 2008). Thus, the effect of estradiol on spine density appears to be time course and paradigm dependent.

OVX decreases spine density in the hippocampus over the course of a few days, an effect that can be reversed with estradiol treatment. Within 24 hours of estradiol treatment, spine density begins to increase. Over the next week, spine density gradually decreases (Woolley and McEwen, 1994). Therefore, it seems estradiol indeed modulates spine density in the hippocampus, but the effect depends on when spines are examined following treatment. As estradiol also modulates responses to drugs of abuse, it is possible that an interaction exists between gonadal hormones and spine density that alters how the body responds to drug exposure.

As estrogens are not the only circulating ovarian hormones, many studies have also examined the role of progesterone. Progesterone treatment following estradiol initially

increases spine density but then induces a decrease in density that is stronger than the effect of estradiol alone (Woolley and McEwen, 1994). Additionally, blocking progesterone receptors inhibits the drop in spine density seen as animals progress from the proestrus to estrus phase of their cycle (Woolley and McEwen, 1994). Overall, the work in the hippocampus indicates that ovarian hormones significantly alter dendritic spine density. In basal conditions, their overall effect fluctuates with estrus cycle stage. Given these results, it seems plausible that the reward system is affected by ovarian hormones, potentially affecting how the brain interacts with drugs of abuse in the future.

Similar results are seen in the medial amygdala, with dendritic spine density also varying throughout the estrus cycle. Decreases are seen during proestrus, estrus, and metestrus. Additionally, males have more dendritic spines than females at baseline in this region (Rasia-Filho et al., 2004). These results also appear to translate to the reward system. OVX females exhibit lower spine densities in pyramidal neurons of the mPFC (Wallace et al., 2006). Estradiol actually decreases spine density in the NAc core and causes deconstruction of spines from more to less mature subtypes in both the NAc core and shell (Peterson et al., 2015; Staffend et al., 2011). Thus, circulating ovarian hormones likely play a large role in how drugs of abuse affect synaptic plasticity. Through altering baseline spine density, ovarian hormones can modulate how the reward system responds to drugs of abuse.

Studies of gonadal hormones and spine density in male animals show a similar trend. Similar to OVX females, castrated males have decreased spine density within the hippocampus. Specifically, evidence consistently indicates that castration decreases spine density in the CA1 region of the hippocampus and the medial preoptic area, an effect that can be reversed with testosterone or dihydrotestosterone (DHT) replacement (Garelick and Swann, 2014; Harley et al., 2000; Hatanaka et al., 2015; Kovacs et al., 2003; Leranth et al., 2003). Again, these results indicate a baseline effect of gonadal hormones on synaptic plasticity in the brain. Within the reward system specifically, it seems that testosterone also influences spine density.

The research on spine density in the NAc also shows striking similarities in males and females. Testosterone treatment to adolescents significantly decreases spine density in the NAc shell, as does DHT treatment to castrated adults (Gross et al., 2018; Wallin-Miller et al., 2016). Though the work on gonadal hormones and spine density in the mesolimbic dopamine system is limited, the existing research shows that testosterone and estradiol likely decrease spine density in the NAc. As changes to neuronal morphology likely influence craving (Christian et al., 2017), it is plausible that gonadal hormone-induced adjustments to spine density underlie sex differences in SUD. Interactions between gonadal hormones and drugs of abuse likely exist to modulate synaptic plasticity in various manners depending on the hormones and drugs that are onboard.

The influence of ovarian hormones on spine density appears to be dependent on glutamate activity. The estradiol-induced alteration of spine density in CA1 pyramidal cells occurs through an NMDA-dependent mechanism (Woolley and McEwen, 1994). Additionally, ovarian hormones alter glutamate receptor binding in the frontal cortex, hippocampus, striatum, and NAc (Cyr et al., 2001). Further, estradiol-induced decreases in spine density

in the NAc core can be blocked with mGluR5 antagonists (Peterson et al., 2015). Estrogen receptor alpha (ERα) functionally couples with mGluR5, which mediates the effects of estradiol on dendritic spine plasticity in the striatum (Grove-Strawser et al., 2010). Cocaine-induced impairments of LTD are likely due to downregulated mGluR5 (Fourgeaud et al., 2004; Knackstedt et al., 2010a; Moussawi et al., 2009) and mGluR5 activation is essential for the actions of estradiol on cocaine-induced behavioral sensitization and self-administration (Martinez et al., 2016; Martinez et al., 2014). Together, these data indicate that estradiol interacts with glutamate to produce the behavioral effects of cocaine. mGluR5 is also involved in opioid reward to some degree, as mGluR5 antagonists inhibit the acquisition and expression of morphine conditioned place preference (Popik and Wrobel, 2002). However, downregulated mGluR2/3 drives opioid-induced impairments to LTD, not mGluR5 (Dong et al., 2007; Robbe et al., 2002). This indicates that interactions amongst opioids, synaptic plasticity, and gonadal hormones likely take a different form than that of cocaine. Given this, it seems likely that differing interactions exist amongst different drugs of abuse, gonadal hormones, and synaptic plasticity that may nonetheless create overlapping behavioral sex differences in SUD.

The role of glutamate in testicular hormone-induced changes in spine density is less clear. It is possible the effects are also glutamate-dependent, as DHT-induced decreases in spine density in the NAc shell similarly depend on mGluR5 activity (Gross et al., 2018). However, developmental increases in hypothalamic spinophilin, a protein that positively correlates with number of dendritic spines, are blocked with an AMPA/kainate antagonist in females but not males (Todd et al., 2007). Therefore, gonadal hormones may similarly modulate spine density in males and females, but through different mechanisms. Given the capability of opioids, cocaine, and gonadal hormones to affect spine density in reward-related brain regions, estradiol and testosterone could modulate synaptic plasticity in a way that affects responses to drugs of abuse. An interaction between drugs of abuse and gonadal hormones might induce sex-specific plasticity in response to cocaine or opioids that might underlie the behavioral sex differences see in SUD.

Conclusion

Though there are FDA approved treatments for opioid use disorder, many are limited in efficacy and there are none currently approved to treat cocaine use disorder. As there are sex differences in treatment outcomes, these therapies are likely limited by factors related to biological sex. Males and females do not develop and experience cocaine and opioid use disorder in the same manner. As females are more vulnerable to many aspects of SUD, biological sex is an important factor to consider in the creation of new pharmacotherapies. Better understanding of the mechanisms driving behavioral sex differences in SUD will ideally lead to more targeted, and thus more effective, pharmaceutical treatments for SUD.

Female vulnerability to cocaine abuse appears to be driven heavily by both organizational and activational effects of ovarian hormones. Fluctuating ovarian hormones throughout the estrus cycle contribute to the enhanced sensitivity to the reinforcing effects of cocaine seen in females (Kippin et al., 2005; Lacy et al., 2016; Lynch, 2008). OVX blunts behavioral responses to cocaine which can be reversed with estradiol replacement (Hu et al., 2004;

Jackson et al., 2006; Lynch et al., 2001; Parylak et al., 2008; Russo et al., 2003; Sircar and Kim, 1999; Walker et al., 2001). Additionally, testosterone appears to be somewhat protective against the behavioral effects of cocaine in males (Chen et al., 2003; Chin et al., 2002). Overall, the behavioral sex differences in cocaine use and abuse appear to be driven predominately by gonadal hormones.

Though similar results have been shown in preclinical models of opioid use disorder (Lacy et al., 2016), OVX studies show a spectrum of results which clouds the role of ovarian hormones in opioid use disorder (Mirbaha et al., 2009; Roth et al., 2002; Sedki et al., 2015; Stewart et al., 1996). Additionally, the role of testosterone in opioid use disorder is unknown. Overall, the existing research indicates that sex differences in opioid abuse might not be driven directly by organizational and activational effects of gonadal hormones. However, the research is limited, and much more work needs to be done in order to draw definitive conclusions.

Cocaine and opioids have divergent effects on synaptic plasticity in the form of dendritic spine density. As gonadal hormones also modulate spine density, it is likely there is an interaction amongst gonadal hormones, drugs of abuse, and synaptic plasticity that may take different forms but similarly drive female vulnerability to SUD. Estradiol replacement can decrease spine density in the NAc core (Sanchez et al., 2012). The decrease in spine density depends mGluR5, which functionally couples with ERα (Grove-Strawser et al., 2010). This coupling mediates the effects of estradiol on dendritic spine plasticity in the striatum (Grove-Strawser et al., 2010; Peterson et al., 2015). As mentioned, cocaine-induced impairments to LTD are likely due to downregulated mGluR5 (Fourgeaud et al., 2004; Knackstedt et al., 2010a; Moussawi et al., 2009). Furthermore, activation of mGluR5 is essential for the actions of estradiol on cocaine-induced behavioral sensitization and self-administration (Martinez et al., 2016; Martinez et al., 2014). This provides a mechanism by which estradiol and cocaine might interact with functionally coupled ERα and mGluR5 to produce the behavioral sex differences in SUD. As opioids and cocaine induce opposing effects on synaptic plasticity, the interactions underlying behavioral sex differences likely do not take the same form. As evidence of this, opioid-induced impairments to LTD are not driven by downregulated mGluR5, but by downregulated mGluR2/3 (Dong et al., 2007; Robbe et al., 2002). This leads to the possibility that opioids act through a separate mGluR2/3 mechanism to drive the behavioral sex differences in SUD.

Differences in synaptic plasticity following cocaine and opioid exposure indicate that the overlapping behavioral effects of cocaine and opioids are likely driven by different mechanisms, possibly through differing glutamate receptors. The lack of effect of ovariectomy in multiple preclincial studies of opioid abuse makes it unlikely that ovarian hormones predominanetly drive sex differences in opioid use disorder. Therefore, it seems that behavioral sex differences in SUD are potentially driven by different mechanisms depending on drug class. Ultimately, more work is needed in order to fully elucidate the mechanisms driving behavioral sex differences in opioid use disorder.

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Highlights

- Females are more vulnerable than males to both cocaine and opioid use disorders
- Sex differences in cocaine abuse are predominantly driven by ovarian hormones
- Sex differences in opioid abuse may not be predominantly driven by ovarian hormones

Table 1.

This table summarizes the studies that have examined the role of ovarian hormones in preclinical models of cocaine and opioid use disorder. The rows for each drug reflect changes to behavioral phenotypes following OVX and OVX + estradiol replacement. The line symbolizes that no studies have examined this directly.

OVX				
	CPP	**Self-administration**	**Seeking**	**PR Responding**
Cocaine	↓	↓	↓	-
Opioids	↓, ↑	No effect	No effect	No effect
OVX + estradiol replacement				
	CPP	**Self-administration**	**Seeking**	**PR Responding**
Cocaine	↑	↑	↑	↑
Opioids	↑, No effect	↑, No effect	↓, No effect	No effect

This table summarizes the studies that have examined the role of ovarian hormones in preclinical models of cocaine and opioid use disorder. The rows for each drug reflect changes to behavioral phenotypes following OVX and OVX + estradiol replacement. The line symbolizesthat no studies have examined this directly