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Frontiers in Neuroendocrinology 29 (2008) 36–47
Frontiers in Neuroendocrinology
www.elsevier.com/locate/yfrne

Review

Sex differences in drug abuse

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Available online 24 August 2007

Abstract

Sex differences are present for all of the phases of drug abuse (initiation, escalation of use, addiction, and relapse following abstinence). While there are some differences among specific classes of abused drugs, the general pattern of sex differences is the same for all drugs of abuse. Females begin regularly self-administering licit and illicit drugs of abuse at lower doses than do males, use escalates more rapidly to addiction, and females are at greater risk for relapse following abstinence. In this review, sex differences in drug abuse are discussed for humans and in animal models. The possible neuroendocrine mechanisms mediating these sex differences are discussed.

Keywords: Addiction; Cocaine; Amphetamine; Alcohol; Opiates; Estradiol; Estrogen receptors

1. Introduction

Drug abuse begins with acquisition or initiation of drug taking and in vulnerable individuals can eventually progress through phases of increased drug taking until an individual is addicted. Sex differences are present for all of the phases of drug abuse, which includes initiation, then escalation of use and the progression to addiction, with subsequent withdrawal followed by relapse [25,80,123,124]. While there are some differences among specific classes of abused drugs, the general pattern of sex differences is the same for all drugs of abuse.

1.1. Sex differences in drug abuse in humans

The rates of drug abuse are currently lower in women than in men. Nevertheless, the number of women using and abusing prescription and illegal drugs is on the rise. Adult men are 2–3 times more likely than women to have a drug abuse/dependence disorder, but this current gender difference may reflect differences in opportunity, rather than vulnerability to drug use [123,124]. If one looks at rate of escalation of drug use, however, women tend to increase their rate of consumption of alcohol, marijuana, opioids, and cocaine more rapidly than do men [17,52,80,84,97]. Furthermore, once addicted to a drug, women can find it more difficult to quit than men do. This is true for nicotine, as well as many other drugs of abuse [6,19,24,80]. Most of the research on sex differences in drug abuse, in both clinical and pre-clinical studies, has investigated the psychomotor stimulants, so opiates, nicotine, and alcohol are grouped together in this overview for convenience.

1.2. Opiates, nicotine, and alcohol

In humans, whether there is a sex difference in the pattern of opiate use has been questioned [80]. Nevertheless, some studies of addicts indicate that women tend to escalate their use of heroin more rapidly, become addicted in a shorter period of time, and seek treatment earlier than men do [3,57].

Women report shorter intervals between cigarettes, and find it more difficult to quit smoking cigarettes than men

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doi:10.1016/j.yfrne.2007.07.003

(reviewed in [80,107]). In a review of 13 studies that looked at the effect of menstrual cycle on smoking cessation, women tend to have a more difficult time quitting depending on the phase of menstrual cycle, with greater craving and dysphoria during the late luteal phase (when estrogen and progesterone are declining) than during the follicular phase of the cycle (when estradiol is low and increasing and progesterone is low) [24]. Women also exhibit a greater negative affective response to a cue that predicts electric shock during nicotine withdrawal, than do men [53]. One possibility for the menstrual cycle effects on smoking cessation is that during the follicular phase estradiol decreases anxiety and negative affect, thereby alleviating some of the negative consequences of smoking cessation. Support for this idea comes from clinical and pre-clinical research showing that estradiol decreases anxiety and enhances positive affect [129].

Finally, fewer women than men abuse alcohol (7–12% vs. 20%). Yet, the frequency that young women are becoming intoxicated on alcohol on a regular basis is rising, and the medical consequences of chronic alcohol consumption are more severe for women than for men. For example, women become addicted to alcohol more rapidly than do men [140], and brain atrophy develops more rapidly in women than in men (other negative medical consequences involve the heart, muscle and liver which are also compromised more rapidly in women than in men [84]).

1.3. Cocaine and the psychomotor stimulants

Cocaine abuse in particular has increased in the last decade among women so that of the 1.8 million Americans who use cocaine, approximately 39.5% are now female [108]. According to this recent report, among users 12–17 years old 51.5% are women, in the 18–25 age group 42.0% are women, and among cocaine users 26 years and older 38.8% are women [108]. The use and dependence among women of stimulant drug use is a growing public health concern in the USA [25,80,133] and in other countries [20,21]. As with other drugs of abuse, evidence suggests that women are more vulnerable to some aspects of psychostimulant abuse.

Women begin using cocaine or amphetamine (AMPH) and enter treatment at earlier ages than men [49,88] and have more severe cocaine use at intake than men [68]. Thus, the progression to dependence may differ between men and women, with women progressing through the landmark stages from initial use to dependence at a faster rate [17,69]. This ''telescoping'' effect reflects a briefer time course for the development of medical consequences and behavioral/psychological factors characteristic of a dependence disorder.

In women, the subjective effects of stimulants vary across the menstrual cycle [64–66]. For example, several of the positive subjective effects of D-AMPH such as euphoria, desire, increased energy, and intellectual efficiency are potentiated during the follicular phase (when estradiol levels are low at first and rise slowly; progesterone levels are low) relative to the luteal phase (when estradiol levels are moderate and progesterone levels are high). Additionally, administration of estradiol during the follicular phase further increases the subjective effects of D-AMPH [65]. In contrast, the subjective effects of psychomotor stimulant drugs are negatively correlated with salivary progesterone levels in women [134], and progesterone administered during the follicular phase has been reported to attenuate the subjective response to repeated self-administered cocaine [42,43,115].

Abstinent women report higher levels of craving following exposure to cocaine-related cues than do men [101], and women have longer periods of use after abstinence than do men [47]. Such differences may be due to sociocultural factors as well as biological factors. Collectively, these results suggest that women may be more sensitive to the addictive properties of cocaine than men. However, this evidence is based primarily on retrospective reports, and relatively little is known about the neurobiological basis for sex differences in motivational processes in general.

1.4. Sex differences in animal models of drug use

Basic research on the role of sex and ovarian hormones in the neurochemical and behavioral responses to acute and repeated exposure to drugs of abuse also finds sex differences and may provide insight into the biological causes of sex differences in drug abuse. While there are sex differences in opiates, nicotine, and alcohol, most of the pre-clinical research has been done with cocaine and other psychomotor stimulants (primarily AMPH), and so this review will focus on the psychomotor stimulants.

1.5. Opiates, nicotine, and alcohol

In laboratory animals, there are sex differences in acquisition, maintenance, and relapse seen with opiates, nicotine and alcohol. The reader is referred to recent reviews for additional information [80,107]. Not all studies find a sex difference in self-administration of opiates (heroin, morphine, and fentanyl). When there is a sex difference, however, females tend to acquire self-administration more rapidly and take more drug during the maintenance phase (see Table 20–1 in [107]). Female rats also acquire nicotine self-administration more rapidly than males, and will work harder to receive nicotine than males (reviewed in [80,107]). So, acquisition of self-administration of opiates and nicotine occurs more rapidly in females than in males.

In laboratory animals, there are sex differences in the development of and recovery from ethanol dependence. Female rats have decreased seizure threshold following withdrawal and have a more rapid return to the control level of seizure susceptibility [34]. Devaud and colleagues have found that ethanol administration affects GABA-A and NMDA receptor subtypes differently in male and female rat brain, and the direction of the sex difference

varies among brain regions [33]. Whether the sex differences in the effects of alcohol and GABA-A and NMDA receptors mediate sex differences in the long-term consequences of alcohol dependence is not known. In mice, sex differences in seizure threshold during ethanol withdrawal is modulated to some extent by ovarian hormones, but there are also inherent sex differences independent of gonadal hormones [1]. It is difficult to characterized sex differences in acquisition of ethanol taking behavior, as rats and mice do not readily self-administer alcohol. Acquisition of ethanol consumption usually involves training animals to self-administer a saccharine sweetened mixture and then fading out the saccharine until animals are taking a pure ethanol solution. This process can take 30 days, making it difficult to parse out factors that influence acquisition. Further research in the clinical setting and the laboratory is needed to clarify the causes and extend our understanding of the nature of these sex differences in alcohol use and abuse.

1.6. Psychomotor stimulants (cocaine and AMPH)

The acute behavioral response to psychomotor stimulants in rodents can reflect both the sex difference and the modulatory role of gonadal hormones in males and females (e.g. [7,13,16,25,36,37,39,40,48,54,56,63,80,112,126]). With repeated exposure to psychomotor stimulants there is an increase in the psychomotor activating effects of the drug, known as behavioral sensitization. Behavioral sensitization can be different in males and females, and can be differentially affected by gonadal steroid hormones, as we now discuss.

Sensitization of AMPH- or cocaine-induced psychomotor behavior can be defined as the absolute increase in the behavioral response exhibited when two tests are compared. Under such comparisons, intact females exhibit more robust sensitization than do intact males [22,23,44,104,105,125]. Following ovariectomy (OVX) of female rats the expression of sensitization to AMPH is attenuated [22,23,44,104,105] or suppressed all together [114,125]. Estradiol treatments in OVX rats enhance sensitization of locomotor activity induced by AMPH or cocaine [44,93]. These results demonstrate that the neurobiological response to stimulant drugs is sexually dimorphic, but they do not address how this biological difference impacts sex differences in the motivation to take drugs.

1.7. Sex differences in stimulant self-administration in animals

The animal model of human drug taking behavior that has the most face validity is self-administration. In self-administration studies, animals are trained to bar-press or nose poke in order to receive access to a drug (usually by i.v. infusion). The animal's pattern of drug taking can be studied during acquisition, maintenance and relapse. It is also possible to manipulate the schedule of reinforcement in order to determine motivation to take a drug.

Sex differences have been reported during all phases of the addiction process as assessed using various self-administration paradigms (see [25,80,107]). When a low dose of drug is used, intact or ovariectomized (OVX) female rats acquire cocaine self-administration at a faster rate than do intact of castrated (CAST) males [26,60,76,78]. Estradiol treatment enhances acquisition of cocaine self-administration in OVX female rats [60,81], but not males [62], and the estradiol antagonist, tamoxifen, when given to intact females inhibits acquisition in intact females [76]. So, there are inherent sex differences independent of circulating gonadal hormones in the acquisition of cocaine self-administration, with females being more vulnerable than males. Furthermore, estradiol enhances acquisition in females, but not in males.

During maintenance conditions, when given a choice between two doses of cocaine, female rats in estrus preferred higher doses of cocaine compared with females in other phases of the estrous cycle or male rats [76,77]. A proposed animal model for the transitional process from use/abuse to addiction is a procedure similar to that developed by Roberts et al. [103]. In this model, known as the ''discrete trial procedure'', animals are housed in self-administration chambers 24 h a day, but they only have access to drug during limited times during the day. With this procedure, female rats 'binge' for a longer initial period of time, take more cocaine over a 7-day access period, and show a greater loss of diurnal control over cocaine intake than do males [82]. When the role of estradiol in 'binge' cocaine intake and subsequent motivational changes is examined, estradiol benzoate (EB) treatment increases the initial binge length and total amount of cocaine self-administered [83]. In one experiment, OVX female rats were tested with and without EB replacement using this procedure (4 trials/h, 1.5 mg/kg/infusion) over a 7-day period. Results revealed that following a 1-day abstinence period, motivation to obtain cocaine was decreased in OVX rats treated with vehicle, but not in OVX rats treated with EB. In another experiment under extended access conditions, using the discrete trial procedure, OVX rats treated with estradiol consumed more cocaine than vehicle treated controls [76]. These results show that estradiol influences both cocaine self-administration under high access conditions and that there are subsequent motivational changes resulting from such access.

When responding for low doses of cocaine is assessed under a schedule in which the number of responses required in order to obtain a cocaine infusion progressively increases, motivation for access to a drug can be assessed. Under this 'progressive ratio schedule' intact female rats reach much higher final ratios than do males, indicating that females are more motivated to obtain cocaine [102]. Females also worked harder for access to cocaine during the phase of the estrous cycle when estradiol was elevated,

suggesting that ovarian hormones modulate the motivation to obtain cocaine [102].

In a recent study from our laboratory we investigated the involvement of ovarian hormones in the motivation to obtain cocaine. We found that estradiol treatment given to OVX rats enhances responding on a progressive ratio schedule at some doses of cocaine (Fig. 1). Compared with OIL treated controls, female rats who received 5 μg EB 30 min before the self-administration session worked harder for access to cocaine at 0.4 and 0.5 mg/kg/infusion, but not at 0.3 mg/kg/infusion (Fig. 1). Thus, there are sex differences in the motivation to take cocaine, and *estradiol enhances the motivation* to take cocaine.

Sex differences have also been observed under reinstatement testing conditions designed to parallel relapse in humans [67,79,107] but see [45]. In a recent study (Fig. 2), we investigated the effect of estradiol in OVX female rats on reinstatement of responding for cocaine.

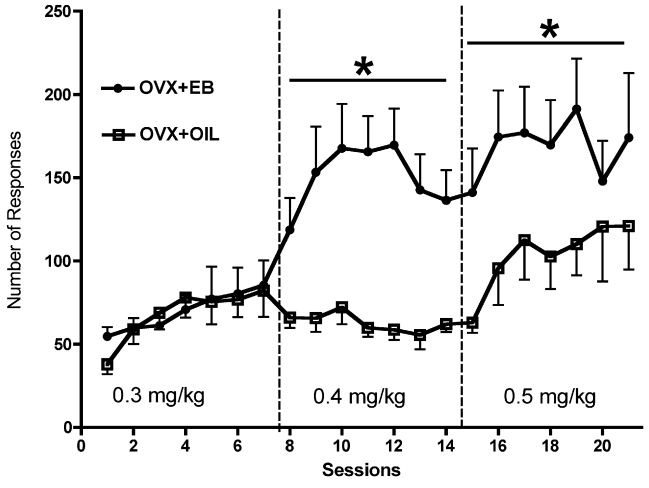

Fig. 1. Effect of estradiol benzoate (EB) on the motivation to obtain cocaine. Ovariectomized (OVX) female rats were prepared for self-administration as previously described [60]. Rats were trained on an FR1 and then an FR2 schedule of reinforcement while receiving 0.4 mg/kg/infusion cocaine, and then were transferred to a progressive ratio (PR) schedule as described by Roberts et al. [102]. Animals were assigned to one of 2 groups: (1) OVX treated with oil 30 min prior to the PR test session for 5 days then no treatment for 2 days (OVX + OIL, $N = 9$); or (2) OVX rats treated with 5 μg EB 30 min prior to the PR session for the first 5 days, and then no treatment for 2 days (OVX + EB, $N = 12$). The mean ± SEM number of responses per 4 h progressive ratio test session is illustrated. During the first week the cocaine dose received was 0.3 mg/kg/infusion, during the second week 0.4 mg/kg/infusion, and during the last week 0.5 mg/kg/infusion. Analysis of variance with repeated measures was conducted at each dose. At 0.3 mg/kg/infusion, there was no difference between the groups. At 0.4 mg/kg/infusion, there was a main effect of Group, $F_{1,19} = 12.27$, $p < 0.0024$; an effect of day, $F_{4,19} = 2.92$, $p < 0.0026$; and a Group by Day interaction, $F_{4,19} = 3.53$, $p < 0.011$. *Post hoc* pair wise comparisons indicated that OVX + EB > OVX + OIL group ($p < 0.001$). At 0.5 mg/kg/infusion of cocaine, there was a main effect of Group, $F_{1,19} = 4.84$, $p < 0.04$; an effect of Day, $F_{4,19} = 6.08$, $p < 0.0003$; but no Group by Day interaction, $F_{4,19} = 0.25$. *Post hoc* pair wise comparisons indicated that OVX + EB > OVX + OIL group ($p < 0.001$). There were no group differences in the number of nose pokes in the inactive hole during any test sessions. *Significant effect of EB on progressive ratio responding as indicated above.

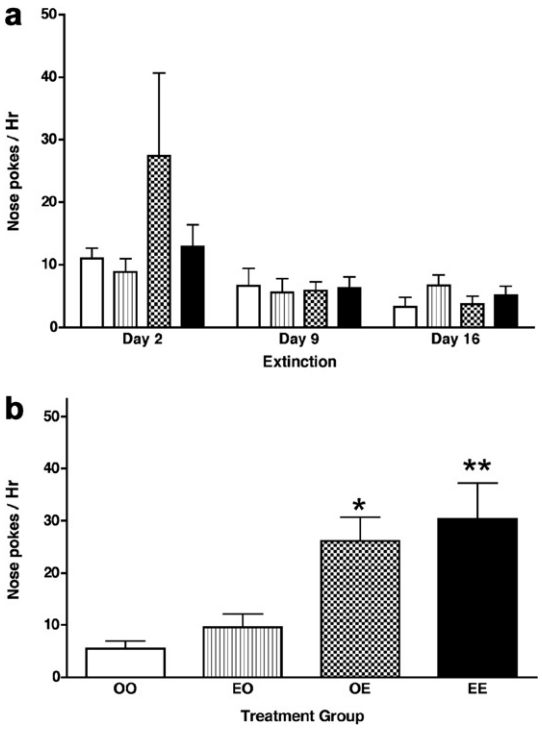

Fig. 2. Effect of estradiol on reinstatement of responding for cocaine. OVX rats were trained to self-administer cocaine with 0.4 mg/kg/infusion cocaine under an FR1 schedule beginning 5 days after catheter surgery using procedures described previously [60]. Animals received 0.1 ml of peanut oil or 5 μg estradiol benzoate (EB, s.c.) in 0.1 μl peanut oil (OIL, s.c.) 30 min before a 3-h self-administration training period. During this three hour training period, the house light and similar paired light + tone conditioned stimuli were present and the syringe was activated to deliver 50 μl of cocaine at the appropriate dose. Daily 3-h sessions of self-administration training were given for 5 consecutive days followed by 2 days off for 2 weeks, animals were required to earn at least 50 infusions per day for the last two consecutive sessions to continue in the experiment. The extinction training was under an FR1 schedule on days 2, 9, 16, and 30 post-training. During this four hour extinction period, the same house light and similar paired light + tone conditioned stimuli were present and the syringe was activated to deliver 50 μl saline. There were no significant differences in the number of infusions received by the different groups during self-administration training and there were no differences among the groups during extinction. (a) On days 2, 9, and 16 after the extinction session, animals received OIL or EB (half of each group received each treatment for a total of 4 groups: OIL during training + OIL during extinction testing [OIL + OIL]; OIL during training + EB during extinction testing [OIL + EB]; EB during training + OIL during extinction testing [EB + OIL]; EB during training + EB during extinction testing [EB + EB]) and were returned to the test chamber for 90 min. No cues were present during the first 30 min, then nose pokes again activated the light + tone and syringe and nose pokes were recorded for 1 h. Open bars = $OVX_{OIL+OIL}$, $N = 11$; gray bars = OVX_{OIL+E}, $N = 7$; Stippled bars = OVX_{EB+OIL}, $N = 7$; and black bars = OVX_{EB+EB} $N = 8$. There were no significant differences in the number of active responses made by animals in these groups after EB priming. (b) On day 30 of extinction, animals received OIL or EB (same groups as above) and were returned to the test chamber. Thirty minutes later animals received 5 mg/kg cocaine and nose pokes were recorded for 1 h. Open bars = OO:$OVX_{OIL+OIL}$, $N = 11$; gray bars = EO:OVX_{OIL+EB}, $N = 7$; stippled bars = OE:OVX_{EB+OIL}, $N = 7$; and black bars = EE:OVX_{EB+EB}, $N = 8$. There was a significant difference in the number of active responses after treatment with 5 mg/kg cocaine ($F_{3,36} = 4.523$, $p < 0.0086$). Subsequent pair wise comparisons indicated that EB treatment prior to cocaine increased responding for cocaine [$OVX_{OIL+EB} > OVX_{OIL+OIL}$ ($p < 0.0294$); $OVX_{EB+EB} > OVX_{EB+OIL}$ ($p < 0.0018$); and $OVX_{EB+EB} > OVX_{OIL+OIL}$ ($p < 0.0126$)]. **$OVX_{EB+EB} > OVX_{OIL+OIL}$ and OVX_{EB+OIL} ($p < 0.01$). *$OVX_{OIL+EB} > OVX_{OIL+OIL}$ rats ($p < 0.03$).

Estradiol [5 μg estradiol benzoate (OVX + EB)] or oil (OVX + OIL) was given 30 min prior to each training session when animals were learning to self-administer cocaine and/or prior to testing following withdrawal from cocaine, and responding for cocaine was measured as an animal model of relapse behavior (see legend for Fig. 2 for more details). In this experiment, animals were trained with a dose of cocaine that both OVX and OVX + EB rats would readily self-administer, so the amount of cocaine received during training did not differ among the groups. Then, animals underwent extinction training on scheduled "withdrawal days", when responding was not reinforced. On days 2, 9, and 16 post-acquisition, animals received an acute dose of OIL or EB (s.c.) to see if hormone treatment or the stress of an injection would re-initiate responding for cocaine (Fig. 2a). There was no effect of OIL or EB on responding, which indicated that the interoceptive cues produced by EB (i.e., any internal sensations produced by estradiol) did not induce rats to respond more for access to cocaine. On day 30, after the extinction procedure, animals received an acute dose of OIL or EB (s.c) and 30 min later received 5 mg/kg cocaine (i.p.; Fig. 2b). Independent of whether acquisition of cocaine self-administration had occurred with EB treatment, animals that were treated acutely with EB during the reinstatement testing exhibited enhanced responding for cocaine compared with animals treated with OIL ($p < 0.03$; Fig. 2b). In a similar experiment, Carroll and colleagues found that acute or chronic estradiol enhanced reinstatement of responding for cocaine [71]. In another experiment, an agonist for estrogen receptor-β (ERβ), but not an agonist for estrogen receptor-α (ERα), was effective at reinstatement of responding when primed with 5 mg/kg cocaine [70]. Only one dose of the agonists were used, so it is possible that higher doses of the ERα agonist might have also been effective. Interestingly, at higher doses of cocaine, responding was re-initiated whether or not the animals were treated the ERβ agonist [70]. Thus, estradiol rapidly enhances the subjective effects of cocaine to reinstate responding for access to cocaine, but estradiol does not reinstate responding on its own.

In contrast to estradiol, progesterone treatment given concurrently with estradiol counteracts the effect of estradiol on acquisition of cocaine self-administration behavior [62]. We have recently confirmed this finding, and shown that progesterone alone does not affect cocaine self-administration, but that progesterone enhances cocaine intake in EB primed OVX rats [139]. Taken together, a wealth of data now indicate that ovarian hormones contribute to sex differences in cocaine self-administration and that estradiol in particular is a key factor influencing the reinforcing effects of cocaine in female rats. So, over the course of the estrous cycle and menstrual cycle, there are peaks and valleys during which females are more or less susceptible to the reinforcing properties of cocaine. The effect of progesterone to counteract the effects of estradiol in some hormone treatment regimens may reflect hormonal influences on maternal behavior, where estradiol and progesterone are elevated during pregnancy and withdrawal from progesterone is necessary for the rapid onset of maternal behavior at parturition.

Castration (CAST) of males has been reported to enhance sensitization of AMPH- or cocaine-induced psychomotor behavior (e.g. [22,23,104]), although this result has not been found consistently [44,125]. It has been hypothesized that if CAST enhances the induction and/or expression of behavioral sensitization, that testosterone treatment should reverse this effect. This is not the case, however, as testosterone treatment has not been found to affect behavioral sensitization in CAST males [44]. Furthermore, there is no effect of CAST on acquisition of cocaine self-administration behavior and a dose of estradiol that enhances self-administration in female rats has no effect on cocaine self-administration behavior in male rats [62]. Thus, the effects of estradiol on the acquisition of cocaine self-administration are sexually dimorphic.

1.8. Mechanisms mediating sex differences and hormone influences in rodents on the response to psychomotor stimulants

1.8.1. Female rat estrous cycle

The female rat has a 4- to 5-day estrous cycle. Circulating estradiol is low during diestrus 1 and increases gradually during diestrus 2 and may persist for a third day of diestrus. The estradiol on these days induces genes needed for initiation of sexual behavior, including induction of progesterone receptors [87]. On the next day, proestrus, there is an endogenous surge of estradiol that occurs around noon, which triggers ovulation about 12 h later. The surge of estradiol is followed in the afternoon by a surge of progesterone which induces behavioral estrus 4–6 h later, coincident with ovulation. Progesterone initially acts synergistically with estradiol to induce sexual activity and is subsequently responsible for the termination of sexual receptivity [87].

Female rats are more responsive to AMPH on the evening of behavioral estrus than 24 h later on diestrus. This is true for the behavioral response to AMPH and for AMPH-stimulated release of dopamine (DA) either *in vitro* or *in vivo* [9–11,14,16,29,30,105]. Intact female rats also tend to show a greater behavioral response to cocaine on estrus compared to other days of the estrous cycle [111] or to males [130]. The basal extracellular concentrations of DA in the striatum, determined by quantitative microdialysis, are greater on estrus than on diestrus [136]. There is also estrous cycle-dependent variation in striatal DA receptors [35,73]. Following ovariectomy (OVX) the response to AMPH is diminished and estradiol is sufficient to rapidly reinstate the response [13].

1.8.2. Male rats

In contrast, in males, there are no differences between intact and CAST males in the efficacy of AMPH, cocaine

or even stimulation of the nigrostriatal pathway to induce rotational behavior or stereotyped behavior [11,15,106]. In studies with acute and repeated cocaine treatment we do not see an effect of CAST on the behavioral response to cocaine or cocaine self-administration [58,60].

1.8.3. Sex differences

In addition to sex differences in the behavioral response to psychomotor stimulants discussed above, there are about 10% more D1 DA receptors in the striatum of male rats than in intact female or OVX rats, but no sex difference in the number or binding characteristics of striatal D2 DA receptors [55,72], although in one experiment female rats had fewer D2 receptors than males [90]. In females, however, estradiol rapidly down-regulates D2 DA receptor binding in striatum [8]. *In vitro*, the AMPH-stimulated increase in striatal DA release is comparable for tissue from intact male rats and intact female rats in estrus [16]. There are sex differences, however, in basal and AMPH-stimulated striatal DA release in the absence of gonadal hormones. Following OVX, the AMPH-induced increase in striatal DA release is significantly less than the response of tissue from CAST [9,16]. On the other hand, in experiments with *in vivo* voltammetry, cocaine or haloperidol induce a greater increase in electrical stimulation evoked extracellular DA in females than in males, possibly due to greater autoreceptor control of the dopamine transporter (DAT) [131,132]. So, there are more D1 DA receptors in striatum of males compared with females, and if there is a sex difference in D2 DA receptors there are more in males than in females, while AMPH-stimulated DA release is comparable in intact males and females during estrus, even though females show a greater behavioral response to AMPH. It is also possible that the ratio of D1/D2 DA receptors plays a role in the behavioral outcome (see Fig. 3).

Results from *in vivo* microdialysis in freely moving rats have found that the basal extracellular concentrations of DA are twice as high in striatum of CAST males as in OVX females, as determined by the no net flux method [136]. So, it could be that the "tone" and/or basal activity of the striatum and NAcc in males and females are different and this means less behavioral activation induced by AMPH or cocaine in males, thus greater increases in DA release would be necessary to overcome the higher basal DA activity and induce behavioral activation or reinforce responding for cocaine. A schematic representation of this is presented in Fig. 3.

Taken with the discussion of the effects of estradiol on cocaine self-administration, it should be pointed out that the addictive properties are not likely to be mediated solely by the effects of estradiol on the ascending DA system. If it were just how much DA activation is produced by a drug, then estradiol should decrease the amount of cocaine consumed, since estradiol enhances DA release. Animals would take less cocaine after estradiol to obtain the optimal amount of DA stimulation, but just the opposite

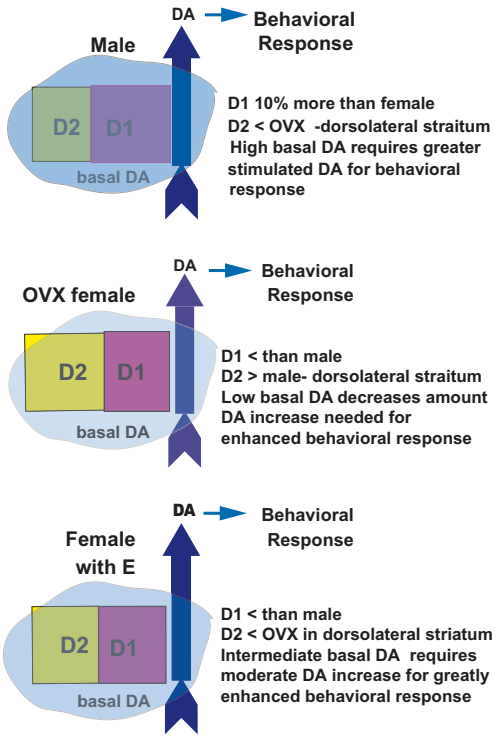

Fig. 3. Schematic of sex differences and the effect of estradiol (E) on the DA system in striatum and NAcc. The pink and yellow squares represent the quantity of D1 and D2 DA receptors (respectively). There are 10% more D1 DA receptors (pink squares) in the striatum and NAcc of male rats than in intact female rats [2,55]. We find greater D2 binding in the dorsolateral striatum of OVX compared to CAST [8], while others have reported no sex differences in D2 binding when the entire striatum is considered [2,55]. Additionally, in females, estradiol rapidly down-regulates D2 DA receptor binding in dorsolateral striatum of female rats [8]. Research from the pair-bonding literature and the drug abuse literature, suggests that D1 receptors decrease affiliative behavior and addictive behavior, while D2 receptors increase these behaviors [4,110]. These D1/D2 effects are thought to be mediated by DA receptors in the NAcc. Here it is proposed that there is a similar relationship between D1/D2 receptors in dorsolateral striatum, that perhaps in concert with the NAcc, contributes to the behavioral effects and addiction liability of psychomotor stimulant drugs. The blue overlay represents the basal DA "tone", the intensity of the color represents the quantity of basal DA, changing the color of DA receptors as their set-point for activation is attenuated by tonic DA stimulation. Results from *in vivo* microdialysis in freely moving rats have found that the basal extracellular concentrations of DA, as determined by the no net flux method, are twice as high in striatum of CAST males as in OVX females. Additionally, basal DA is greater in estrous females than in diestrous females suggesting that estradiol enhances basal DA "tone" [136]. The stimulated release of DA is represented by the blue arrows, where the darkness of the arrow color is proportional to the amount of release (male = females > OVX in dialysis; females > males). In experiments with *in vivo* voltammetry, cocaine or haloperidol induce a greater increase in electrical stimulation evoked greater extracellular DA in females than in males, possibly due to greater autoreceptor control of the dopamine transporter (DAT) [131,132]. *In vitro*, the AMPH-stimulated increase in striatal DA release is comparable for tissue from intact male rats and intact female rats in estrus, and release is attenuated after OVX [16]. The consequence of the coordinated effect of DA stimulation and receptor activation is a behavioral response/rewarding effect that is greatest in females with OVX + E (or intact females in estrus) > OVX > males. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

occurs. Estradiol enhances the motivation to take cocaine, so in addition to the enhancement of DA release, the neural systems that respond to the increase in DA must be sexually dimorphic and/or modulated by estradiol so that greater DA stimulation is reinforcing. We suggest that sex-related differences in striatal DA release and receptors reflect an underlying sexual dimorphism in the striatum and NAcc. The concept that activation of the striatum by psychomotor stimulants is sexually dimorphic is supported by the results of a study that examined Fos-immunoreactivity in striatum of CAST and OVX rats after treatment with AMPH [30]. This study found that the pattern of Fos expression differed for males and females, so the areas of the striatum (and presumably downstream areas) activated by AMPH are sexually dimorphic.

1.9. Mechanisms mediating the effects of estradiol on the striatum of female rats

The acute administration of estradiol to OVX rats (but not CAST males) induces a rapid increase in AMPH-induced striatal DA release as detected by *in vivo* microdialysis [10,28]. Estradiol also induces an increase in striatal DA turnover [38] and, as mentioned above, down-regulates D2 class DA receptors [8]. This sex difference in the effect of estradiol is thought to be due to the direct effect of estradiol on the striatum, as physiological concentrations of estradiol *in vitro* enhance the AMPH- or K^+-induced release of DA from striatal tissue in superfusion [9], and interfere *in vitro* with the GTP-induced affinity shift of D2 receptors [74]. In cultured striatal neurons from embryonic mouse, estradiol induces changes in adenylate cyclase activity stimulated by D1 and D2 DA receptor agonists by apparently modifying the G-protein coupling process [85,86]. Furthermore, the pulsatile administration of physiological concentrations of estradiol to striatal slices directly stimulates DA release *in vitro* [9]. Thus, estradiol acts directly on the striatum to induce changes in DA release and DA receptor activity.

Estradiol has also been shown to act directly on the NAcc to enhance K^+-stimulated DA release [117,119]. Local injection of 20–50 pg 17β-estradiol, but not 17α-estradiol, produces a rapid (within 2 min) and dramatic increase in stimulated DA overflow detected by *in vivo* voltammetry [120]. We have also seen enhanced cocaine-induced DA in dialysate from the striatum of OVX rats 30 min after estradiol treatment [59]. Although there has been less research on estradiol-DA interaction in the NAcc, the work of Thompson and Moss [116–118,121,122,135], and our own work suggests that the mechanism(s) mediating the effects of estradiol in the NAcc and striatum are similar.

Electrophysiological studies have shown that estradiol can induce rapid changes in the response of striatal neurons to D1 and D2 agonists [32]. Results from whole cell clamp studies in acutely dissociated striatal neurons indicate that there are rapid effects of estradiol to decrease current through Ca^{2+} channels in medium spiny (i.e., GABAergic) striatal neurons [89]. The effects are rapid (within seconds), reverse as soon as estradiol delivery ceases, are sex specific (cells from females respond to much lower doses of estradiol than do cells from males), and are seen at physiologically relevant concentrations of estradiol. Furthermore, estradiol conjugated to bovine serum albumin (E-BSA, prevents estradiol entry onto cells) is also effective, while estradiol applied internally to cells through the electrode is not effective at reducing Ca^{2+} currents, nor does it block the effect of 1 pM estradiol applied externally. Collectively, these results suggest that the effect of estradiol occurs at the external membrane surface. In the presence of GTPγS (which prevents inactivation of G-protein mediated events) the effect of 17β-estradiol does not reverse when hormone delivery ceases. Thus, the effect of estradiol is dependent upon a G-protein coupled receptor. Finally, the effect of 17β-estradiol is stereospecific and sex-specific. We find that 17α-estradiol does not mimic the modulation, and steroid specific as 100 pM estrone and 3-methoxyestriol were ineffective while estriol and 4-hydroxy-estradiol mimic the effect of 17β-estradiol. Furthermore, in striatal cells from males there was no effect of 17β-estradiol at concentrations that were effective in females. We conclude that estradiol has rapid stereospecific effects on striatal neurons in females that alter signaling pathways by acting at a receptor on the extracellular membrane [89].

In *in vitro* superfusion experiments we have found that the effects of estradiol on AMPH-induced striatal DA release from tissue obtained from OVX females is mimicked by the catecholestrogens or E-BSA, but not by diethylstilbesterol (DES), estriol or estrone [137], Furthermore, the effect of estradiol to enhance AMPH-induced DA release from striatal tissue *in vitro* is blocked by the estradiol receptor antagonist ICI 182,780, but not by tamoxifen [138]. E-BSA mimics the effect of estradiol to enhance AMPH-induced DA release. Thus, the pharmacology of the effects of estradiol in the striatum indicate that it has a steroid-specific and stereo-specific effect. Hydroxylation of the A ring does not inhibit this effect, while modification of the D ring prevents efficacy of a compound in the striatum at mERa. Finally, estradiol need not enter a cell to produce its effect in the striatum.

Due to the results of the studies described above showing effects of estradiol on GABAergic neurons, we hypothesize that estradiol's effect on striatal DA release is mediated indirectly by the effect of estradiol on intrinsic striatal neurons that release GABA. We have recently demonstrated that 30 min following estradiol treatment, the increase in GABA concentrations in dialysate induced by a depolarizing concentration of K^+ in the striatum is significantly attenuated, compared with vehicle-treated controls [61]. These results support the idea that estradiol is rapidly inhibiting striatal GABA release, and suggest that enhancement of DA release following estradiol is mediated (at least in part) by a release of inhibition.

1.10. Evidence that ERα is also a membrane receptor for estradiol

Evidence that the classical receptors for estradiol (ERα and ERβ) may be found in the cell membrane and mediate the rapid responses to estradiol (i.e., mERα and mERβ) in female rats come from a variety of sources. A number of immunocytochemical studies have demonstrated that antibodies to ERα will bind to the exterior of the cell. Watson and colleagues have shown that seven different antibodies to ERα bind to the membrane of rat pituitary tumor cells and antibodies that bind to the hormone-binding domain of ERα modulate rapid E-induced prolactin release [92]. In the hippocampus estradiol regulates the subcellular distribution of phosphorylated Akt in hippocampal CA1 dendrites [141] and there is ultrastructural evidence that there are ERα receptors in axons and synaptic terminals of CA1 [51,91].

When the classical receptors ERα and ERβ are transfected into fibroblasts, Chinese hamster ovary (CHO) cells or neuroblasts, a certain proportion of the receptors are found in the cell membrane where they confer rapid responses to estradiol [99,100,127]. In CHO cells in culture, transfection with ERα or ERβ results in ER being expressed in the cell membrane and activation of rapid G-protein signaling systems in response to estradiol stimulation [100]. In peripheral cells ''mERα'' has been shown to be present in association with the protein caveolin, in discrete caveoli domains of the plasma membrane [99]. Caveoli are 'cave-like' structure in which various receptors and signaling molecules are sequestered. These include G-proteins, tyrosine kinases, and threonine–serine kinases [98]. It is hypothesized that caveolin associates with mERα and facilitates its movement to the membrane and anchor the receptor in the caveoli. [99]. This organization of signaling molecules and receptors allows mERs to modulate a variety of signal transduction cascades in target cells. In fibroblasts and neurons in culture, estradiol activation of MAP kinase signaling systems has been found after transfection with ERα or ERβ [113,127,128]. Taken as a whole, these results support the idea that the classical ERs (ERα and ERβ) are acting at the membrane to confer rapid responses to estradiol in the brain, as has been demonstrated peripherally and in model systems.

Membrane receptors, distinct from ERα or ERβ, that respond to estradiol have also been identified in the brain. In the arcuate nucleus of the hypothalamus a G-protein coupled receptor that is involved in energy homeostasis has been reported [94], and the orphan G-protein coupled receptor, GPR30, has been found to mediate rapid responses to estradiol in the hippocampus [46]. Whether these receptors are found in the reward system has not yet been examined. Nevertheless, evidence that estradiol rapidly enhances striatal DA release and the motivation to take cocaine supports the idea that the mER's may play a role in the effects of estradiol on drug taking behavior.

1.11. Possible chromosomal mechanisms underlying sex differences in drug abuse

Most sex differences in the brain are thought to be due to the effects of gonadal hormones during development and/or in the adult mammal [5,18]. Recently, sex differences have also been found that can only be accounted for by the complement of sex chromosomes (XX vs. XY) alone or in combination with gonadal hormone influences [12,27]. Such potential contributions become most evident in cases where sexual phenotype appears to be insensitive to the effects of sex hormones during development or in cases where sex differences develop before the onset of sex-specific patterns of gonadal secretions [12,31,109]. Until recently, determining the influences of gonadal hormones and sex chromosome complement was extremely difficult. However, mouse models are now available in which gonadal hormone status (ovaries vs. testes) is independent of sex chromosome complement (XX vs. XY; [31]). Mice with a deletion of the testis-determining *Sry* gene from the Y chromosome develop ovaries even when the Y chromosome is present. Absence of the *Sry* gene in these mice (XY^-) as well as in normal females (XX) results in the development of ovaries and a gonadally female phenotype [75]. These mice allow independent assessment of the influences of gonadal hormones and sex chromosome complement on the neurobiology of sex differences in both normal and pathological behavior [31]. Using this model, habit formation has been found to be affected by sex chromosome complement, independent of gonadal hormone status [95]. Specifically, XX mice acquired a food-reinforced habit faster than XY mice, independent of gonadal hormone status. In another study, female mice show greater locomotor sensitization to cocaine compared to males [96], replicating the previous literature [50,125]. Critically, this effect depended upon the gonadal hormone status rather than sex chromosome complement [96]. So, habit formation, but not behavioral sensitization to cocaine, may be influenced by sex chromosomes. Clearly, sexual dimorphism in the development of habit formation could have important implications for drug addiction.

In another experiment using this animal model, the effect of sex chromosome complement on brain stimulation reward (BSR) and potentiation of this behavior by AMPH was characterized using a rate-frequency protocol [41]. There were no differences in BSR as measured by the amount of current or frequency required to sustain responding. Interestingly, AMPH potentiated BSR in mice with XY genotypes, but not in mice with XX genotypes, regardless of -sry expression during development. It was concluded that AMPH potentiation of BSR in XY individuals but not XX individuals may reflect the differences in the sensitivity of the DA system neurons caused by group differences in X- or Y-linked genes [41]. An important question remains as to how genetic sex and/or hormonal differences interact and whether differences in the biology of motivational function can explain sex differences that

promote uncontrolled and disregulated patterns of intake that are the hallmark of addiction.

2. Conclusions

From this brief discussion it should be clear that there are sex differences in drug abuse. There are still significant gaps in our knowledge, due to the lack of empirical data that would be generated from a systematic approach to the topic. We know very little about sex differences in marijuana use, for example, in humans or in animal models. The research on sex differences in opioids use and in alcohol are also lacking in sufficient data to draw strong conclusions. Thus, there is substantial need for additional experimental data generated from testing specific hypotheses about the neural bases for sex differences in drug abuse.

Studies of the response to cocaine in gonadectomized male and female rats provide the strongest data regarding the neural evidence for sex differences in drug abuse. These data indicate that there is an underlying sex difference due to sexually dimorphic development of the brain that, in part, mediates the sex difference in drug abuse. Studies from mice in which the testes-determining *Sry* gene is deleted from the Y chromosome and inserted in an autosome indicate that these sex differences in motivation may, at least in part, be genetic in origin. In addition, there are effects of gonadal hormones that modulate the neural systems that mediate drug taking behaviors. In particular, estradiol enhances the motivation to take drugs, while progesterone can counteract the effect of estradiol. Ultimately research on the neurobiological mechanisms of sex differences in drug abuse will aid in improved treatment and understanding of drug abuse in both females and males.

Acknowledgments

These studies were supported by a grant from the USPHS National Institute on Drug Abuse DA12677 to J.B.B. Ming Hu was supported by UMSARC training grant. We thank Brandon Luma for excellent technical assistance. All experimental results reported were conducted according to a protocol approved by the University Committee for the Use and Care of Animals at the University of Michigan.

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