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Review

Sex differences in the vulnerability to drug abuse: a review of preclinical studies

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Abstract

Clinical and preclinical findings indicate that males and females differ on several aspects of drug reinforcement. Females are more vulnerable than males during transition periods of drug use that are characteristic of drug addiction and relapse. Females are also more sensitive than males to the reinforcing effects of stimulants. It has been suggested that ovarian hormones contribute to the mechanisms of action underlying these sex differences. This review examines the preclinical literature on sex differences and ovarian hormonal influences on drug self-administration in animals. It summarizes the findings on the effects of these variables during different phases of drug addiction. Possible differences in the mechanisms of action of drugs of abuse due to interactions with sex differences or ovarian hormonal factors are considered. The animal literature on sex differences in drug abuse treatment effectiveness is also discussed.

Keywords: Addiction; Animal models; Drug abuse; Estrogen; Gender; Ovarian hormones; Progesterone; Self-administration; Sex differences; Treatment

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1. Introduction

Results from epidemiological studies have generally suggested that the majority of drug abusers are males. The number of clinical studies in which sex differences in drug abuse were investigated has steadily increased, and recent prevalence rates indicate that the number of female drug abusers is increasing [1]. The clinical literature has suggested that females differ from males in their biological and subjective responses to several abused drugs. For example, females initiate cocaine use sooner, become more intoxicated after similar levels of alcohol intake, and take less time to become addicted to cocaine, opioids, and alcohol after initial use than males [2,3]. Females also report higher rates of cocaine use and shorter periods of cocaine abstinence than males [4].

The results from the clinical studies mentioned above are mirrored in recent preclinical studies. For example, female rats tend to be more vulnerable to stimulant self-administration during transition states of addiction such as acquisition of drug taking behavior [5–8], shifts from controlled to uncontrolled drug intake [9], and reinstatement of drug-seeking behavior (e.g. relapse) [10]. It has also been suggested that drug-taking behavior in female rats [11,12] and monkeys [13,14] is reduced to a greater extent than in males by pharmacological and behavioral treatments for drug abuse.

Reasons for sex differences in drug abuse are not yet clear. It is possible that, in humans, these differences may reflect changing sociocultural standards [1–3]. It has also been suggested that ovarian hormones contribute to the sex differences observed in humans and animals [15,16]. Animal models of drug self-administration are important in determining the cause of sex differences in drug abuse, as they provide controlled environments in which the subject self-administers the drug. This control eliminates sociocultural and other factors that may occlude sex differences in clinical studies of drug abuse. Also, conclusions from animal studies are critical in determining what factors are important to investigate in clinical studies.

The primary purpose of this review is to provide a detailed discussion of the preclinical literature examining sex and ovarian hormonal influences on drug

self-administration. This review also includes a discussion of potential sex differences in mechanisms of drug action, and drug abuse treatment effectiveness.

2. Sex differences in drug self-administration

Animal models that simulate different phases of drug abuse (e.g. acquisition, maintenance, regulation/dysregulation, and relapse) and the transitions from one phase to another [17] will be considered in Section 2.1. It is important to use animal models to look at aspects of drug abuse for a number of reasons. For example, it is nearly impossible to study the initiation of illicit drug use in drug-naïve humans, except by retrospective self-report and long-term epidemiological studies. Therefore, experimental studies of acquisition of drug self-administration in drug-naïve animals are important for investigating factors that affect vulnerability to initiation of drug use in humans [18]. Analyses of steady-state maintenance levels of drug intake are often conducted using animal models of drug abuse that employ progressive ratio (PR) schedules and/or behavioral economic measures to determine the reinforcing effectiveness of the drug [19]. Additionally, modeling the escalation from steady-state maintenance patterns of drug intake to dysregulated and accelerated patterns of drug intake provides information about the loss of control that is characteristic of human drug addiction. The reinstatement of regular drug use following a period of abstinence (e.g. relapse) is one of the most challenging aspects of drug abuse to control and/or treat; therefore, animal models of relapse (e.g. reinstatement) are of particular importance due to the ethical difficulties of studying this phase of addiction in humans, as abstinent former drug users would be likely to reinitiate drug use when exposed to priming conditions [18]. There is always the question of whether animal models adequately represent and predict human behaviors; however, several of the models discussed here have been validated by parallel findings in human laboratory studies [5–14]. Table 1 summarizes the preclinical studies on sex differences during different phases of addiction.

Table 1
Summary of rodent (except, where otherwise noted) studies examining sex differences in drug self-administration

Drug	Phase	General finding	Citation[a]
Caffeine	Maintenance	F>M choice test	[21]
Cocaine	Acquisition	F>M %, F<M rate	[5]
		F<M rate	[7]
		F>M rate	[20]
	Maintenance	F>M BPs (PR)	[7,26,27]
		F=M choice test	[24]
		F>M choice test	[22]
		F>M FR 1	[5]
		F>M dysregulation	[9,27]
		F=M FR 5	[20]
		F>M escalation	[31]
	Relapse	F>M reinstatement	[10,27]
Methamphetamine	Acquisition	F>M %, F<M rate	[8]
	Maintenance	F=M FR 1	[8]
		F>M BPs (PR)	[8]
Nicotine	Acquisition	F<M rate	[6]
	Maintenance	F>M BPs (PR)	[6]
		F>M choice test	[23]
Heroin	Acquisition	F=M	[32]
		F<M rate	[5]
	Maintenance	F=M BPs (PR)	[32]
		F=M FR 1	[5]
		F>M FR 1	[33]
		F>M FR 4	[37]
		F>M BPs (PR)	[37]
Morphine	Maintenance	F>M choice test	[34,35]
		F=M choice test	[39]
		F>M BPs (PR)	[37]
		F>M FR 4	[37]
Methadone	Maintenance	F=M (monkeys) choice test	[38]
Fentanyl	Maintenance	F>M BPs (PR)	[36]
	Relapse	F>M reinstatement	[36]
Alcohol	Acquisition	F=M (monkeys)	[40,41]
	Maintenance	F=M choice test	[24]
		F>M choice test	[44–50]
		F>M (monkeys) intake frequencies	[43]
		F<M (monkeys)	[42]
PCP	Acquisition	F>M % (monkeys)	[51]
	Maintenance	F=M (monkeys) FR 4–128	[14,38]
		F>M escalation	[52]
		F<M withdrawal	[53]
Pentobarbital	Maintenance	F=M (monkeys) choice test	[38]

[a] Citations listed are representative references discussed in the review.

2.1. Stimulants

2.1.1. Acquisition

It has been consistently reported that a greater percentage of female rats acquire stimulant self-administration compared to male rats, and they do so at a faster rate than males. This has been demonstrated with cocaine [5,7], and methamphetamine [8] in our laboratory and nicotine in another laboratory [6]. It should be noted that low doses of stimulants were used in the above studies. Recently, Caine and coworkers [20] reported that male rats acquired cocaine self-administration in significantly fewer days than female rats. In this study, a relatively high dose of cocaine (1.0 mg/kg/injection) was used as opposed to the above studies [5,7] that used a lower cocaine dose (0.2 mg/kg/injection). It should also be noted that under the condition that implemented a high dose of cocaine [20], ceiling effects occurred (e.g. 100% of male and female rats acquired drug self-administration in less than 20 days). This may have obscured any differences in the percentage of animals in each group that acquired cocaine self-administration. In an earlier study with nicotine there were no sex differences in acquisition when higher doses were used [6]. Therefore, it

appears that low doses of stimulants more readily avoid ceiling effects during acquisition, and they provide optimal conditions for observing sex differences.

2.1.2. Maintenance

The literature examining sex differences during the maintenance phase of stimulant self-administration is less consistent than that for acquisition. Female rats consumed more caffeine in mg/kg of body weight compared to males [21], and female rats that had previously shown an increased rate of acquisition of cocaine self-administration maintained higher levels of cocaine intake (mg/kg) than males under a fixed ratio (FR) 1 schedule of reinforcement [5]. However, no significant sex differences were found during the maintenance of methamphetamine self-administration under an FR 1 schedule in rats that had exhibited sex differences during the acquisition of methamphetamine self-administration [8]. In another study, female mice consumed more oral cocaine solution than males when both cocaine and water were concurrently available [22] and more saccharin-flavored oral nicotine compared to males when a saccharin-only solution was concurrently available [23]. However, results from another study indicated no sex differences in oral cocaine consumption in rats [24]. More recently, sex did not alter the shape or position of dose–response functions for cocaine self-administration under an FR 5 schedule in rats [20]. Overall, it appears that low FR schedules are not sensitive to sex differences in the reinforcing effects of drugs, and inconsistent findings have been reported.

Sex differences in stimulant self-administration are more apparent under more challenging behavioral schedules of reinforcement (e.g. PR). Under PR schedules, the break point (BP), which represents the final ratio (responses/drug delivery) of lever responses reached (in a series of increasing ratios) by the animal in order to earn one delivery of drug, is used to measure the reinforcing effectiveness of the drug [25]. Female rats reached significantly higher BPs than males under a PR schedule for nicotine [6], cocaine [7,26,27], and methamphetamine [8] self-administration.

2.1.3. Regulation/dysregulation

Sex differences have been examined in the escalation from steady-state maintenance patterns of drug intake to dysregulated and accelerated patterns of drug intake. In one study, a two-lever self-administration procedure that allowed animals to control both the dose size and interdose interval of the drug infusion was used, and dysregulation was defined as a lower correlation between these two variables [28]. The results showed that after stable responding for cocaine was achieved, the regulation of cocaine intake was disrupted more in females than in males [9]. In another study, dysregulation of cocaine intake was generated by giving rats access to self-administration for 24-h/day (4, 10 min trials/h) for 7 days. Under these conditions, females self-administered higher levels of cocaine for longer initial periods of time, and showed a greater disruption in diurnal control over intake than males [27]. Data from our laboratory also indicated that female rats escalated their cocaine intake to a great extent than male rats following an escalation procedure [29,30] that extended self-administration access conditions from 1 to 6 h/day [31].

2.1.4. Reinstatement

There have only been two studies that have assessed sex differences in the reinstatement (e.g. relapse) of stimulant self-administration in rats [10,27]. In one of these studies a priming model of reinstatement was used in which lever pressing for cocaine was extinguished and responding for saline was measured following cocaine priming injections [10]. In this study, the female rats displayed a higher rate of drug-seeking behavior than males following a priming injection of cocaine, and responding was reinstated at a lower cocaine-priming dose in females than in males [10]. In the other study, male and female rats had access to cocaine self-administration under a 24-h/day discrete trial procedure (4, 10 min trials/h) for 7 days. Subsequently, rats were put on a PR schedule for three sessions and after that they were not allowed access to cocaine self-administration for 10 days. After the abstinence period, female rats responded at higher levels under a PR schedule to obtain cocaine infusions than did males. These results concurred with the earlier study that female rats are more vulnerable than males to the reinstatement of cocaine-seeking behavior [27].

2.2. Opioids

2.2.1. Acquisition

Sex differences in the acquisition of opioid self-administration are equivocal. In one study, no sex differences were reported [32]; however, in another study female rats acquired heroin self-administration in significantly fewer days compared to male rats [5]. In another study female rats self-administered more heroin than males during both food restriction and satiation conditions during acquisition [33]. Procedural differences, such as differential length of self-administration sessions, drug doses, and feeding conditions may have contributed to the inconsistent results.

2.2.2. Maintenance

Regarding the maintenance of opioid self-administration, female rats displayed greater levels of oral morphine [34,35], oral fentanyl [36], and i.v. heroin [33] intake than male rats. Cicero and coworkers [37] also reported that female rats consumed significantly greater amounts of i.v. heroin and morphine at lower doses, and they reached higher BPs for the drugs compared to male rats. However, no sex differences were reported in oral methadone consumption in monkeys [38]. In rats, no sex differences were reported in the maintenance of heroin self-administration using a simple

FR 1 schedule [5] or a more challenging PR schedule [32]. There were also no significant sex differences reported in morphine preference in both morphine preferring (C57BL/6J) and morphine avoiding (DBA/2J) mice [39], the results with opioids suggest that several factors (route of administration, dose, schedule) are related to sex differences in opioid self-administration.

2.3. Ethanol

2.3.1. Acquisition

Sex differences in the acquisition of ethanol self-administration have been investigated in two laboratory studies using nonhuman primates. Pakarinen and coworkers [40] examined the acquisition of ethanol self-administration in juvenile male and female rhesus monkeys, and they did not find a significant sex difference. However, they did find a significant interaction between sex, ethanol concentration and feeding condition. Additionally, Grant and Johanson [41] did not find a sex difference in the acquisition of ethanol self-administration in adult rhesus monkeys.

2.3.2. Maintenance

During the maintenance phase of self-administration in nonhuman primates, females consumed less [42] ethanol in g/kg body weight relative to males using operant conditioning methods. However, using home-cage drinking tests, Juarez and coworkers [43] reported that female monkeys showed a greater frequency of alcohol intake than males. In rodent home-cage ethanol drinking studies, female rats maintained greater levels of ethanol intake than males [44–47]. Additionally, female rats had a greater preference for ethanol over water (5% ethanol/total fluid) compared to males, drank more ethanol (g/kg), and when the ethanol was doubled in concentration (10%) females increased their ethanol intake, while males titrated their intake to consume the same as when 5% ethanol was available [48]. Dess and coworkers [46] showed that female rats selected for higher levels of saccharin intake (HiS) consumed more ethanol than HiS males. Sluyter and coworkers [49] found that female rats selected for high susceptibility to morphine (APO-SUS) consumed more ethanol than APO-SUS males. Wild-type female mice also consumed more ethanol than wild-type male mice, and genetically altered (G-protein-coupled inwardly rectifying potassium channel (GIRK2) knock-out) female mice consumed more ethanol than their male counterparts [50]. However, in one study no sex differences in oral ethanol intake in rats were reported [24].

Although sex differences were reported in the studies described above during the maintenance of ethanol consumption, it should be noted that home-cage, two-bottle drinking tests were used in these studies, and when operant conditioning methods are used (response-contingent drug delivery), there are often no sex differences during maintenance [38,42]. Thus, two-bottle drinking tests may be more sensitive to sex differences than operant methods that have a relatively low response requirement.

2.4. Other drugs

2.4.1. Acquisition

Sex differences in the acquisition of orally self-administered PCP have been examined in one study using rhesus monkeys. In this study, Carroll and coworkers [51] reported that 100% (7/7) of a group of drug-naïve female rhesus monkeys acquired self-administration of a low dose of phencyclidine (PCP), while only 36.4% (4/11) of a drug-naïve male group met the acquisition criterion.

2.4.2. Maintenance

There have only been a few attempts to examine sex differences in the maintenance of other drugs of abuse. No sex differences were reported in maintenance levels of PCP intake (mg/kg) in nonhuman primates [37,14], although there were differences during the acquisition phase [51]. Additionally, female and male monkeys consumed similar amounts (mg/kg) of orally self-administered pentobarbital [38]. However, preliminary data have shown that following extended access (e.g. 6-h) to orally self-administered PCP, female monkeys escalated their PCP intake to a greater extent than male monkeys under both an FR 16 schedule, and subsequently under a PR schedule. This was reflected in the females' dose–response function being elevated above the males [52]. Additionally, under a procedure that had previously been reported to determine physical dependence to PCP in monkeys, female monkeys showed only slight withdrawal-induced reduction in food intake even though their prior PCP intake (mg/kg) was comparable to that of the male monkeys that did exhibit a greater magnitude of withdrawal-induced food reduction [53].

2.5. Summary

The animal literature indicates consistent sex differences during the acquisition phase of stimulant self-administration. However, sex differences during the acquisition of self-administration of other abused drugs are equivocal. It is important to note that dose of drug is an important factor when investigating sex differences in the acquisition of drug self-administration, and sex differences are more apparent when low doses of drugs are used [5,6,33]. During maintenance conditions that require the animal to emit a low number of responses for a reinforcer (e.g. FR 1), the male/female difference is either diminished in magnitude with some drugs such as cocaine [5], or not statistically significant with other drugs such as heroin [5], nicotine [6], or PCP [14]. Under more challenging behavioral schedules such as a higher FR or PR schedule, sex differences are more consistently revealed with the females' behavior exceeding the males' [6,8,26], and the schedule differences are also magnified at lower drug doses [6,8]. Sex differences in

relapse were reported with cocaine, with females exhibiting greater extinction behavior and higher levels of reinstatement after a cocaine priming injection, but relapse to ethanol and other drugs of abuse has not yet been examined. Therefore, more studies are needed to determine whether this effect extends to other classes of drugs.

3. Influence of ovarian hormones in drug self-administration

When considering the mechanisms of action of underlying sex differences in drug abuse, it is important to consider gonadal hormones. These hormones include testosterone in males and estrogen and progesterone in females. The effects of testosterone on drug effects have been studied in animals [54–56], but the results are inconclusive. The literature is more consistent in showing that ovarian hormones are related to the sex differences observed in drug abuse; therefore, this review will focus on the female ovarian hormones estrogen and progesterone.

Ovarian hormonal fluctuations across the menstrual cycle have been well characterized in humans and nonhuman primates; however, there are no conclusive data that describe the relationship between phases of the rodent estrous cycle and phases of the menstrual cycle. At the present time it is not clear how well the rodent data fit that obtained from humans and nonhuman primates. Therefore, the determination of the relationship between the rodent and primate (human and nonhuman) reproductive cycles would allow for a more complete generalization from data examining the influences of ovarian hormones on drug-induced behaviors and drug self-administration from one species to another. It would also allow researchers to determine whether or not the primate and rodent hormonal systems are fundamentally equivalent in their impact on drug abuse, and whether or not results from studies using rodent models can be generalized to clinical data.

One important difference between the rodent and nonhuman primate reproductive cycles is length. In nonhuman primates (and humans) the menstrual cycle lasts an average of 28 days [57], while in rodents the estrous cycle lasts an average of 3–5 days [58]. Also, the length of each particular phase in the reproductive cycle varies between rodents and primates. For example, each menstrual cycle phase in primates can last between 5 and 14 days [59], whereas, each estrous cycle phase in rodents only lasts between 6 and 57 h [60]. This creates difficulty in correlating behavioral observations with estrous cycle phase in female rodents. Conversely, the length of each menstrual cycle phase in nonhuman primates is fairly long and allows for behavioral correlates with phase of the cycle. Another difference between the menstrual and estrous cycles is the occurrence of 2 vs. 1 peaks in estrogen levels during the menstrual vs. estrous cycle, respectively. Specifically, the largest increase in estrogen occurs during the follicular phase and a relatively smaller increase occurs during the luteal phase of the menstrual cycle. Therefore, estrogen may be exerting its effects on drug reinforcement at two different menstrual cycle phases in primates; whereas, in rodents only one phase of estrous contains an estrogen surge (i.e. proestrus).

Two paradigms are typically used in experimental studies on the influence of ovarian hormones on drug self-administration in animals. The first is to use phase of the estrous cycle as the independent variable and assess the dependent measures according to which phase the animal is in. Potential problems with this approach are that the drug of interest (e.g. cocaine), or other conditions [61] such as housing (with/without males, individual/group) or stress may alter the estrous cycle [62]. Thus, it may be difficult to examine drug effects in a hormonally normal animal. The second method is to surgically remove (e.g. ovariectomy), or chemically block (e.g. administration of a hormone antagonist) the secretion of estrogen and/or progesterone, and administer exogenous ovarian hormones after ovariectomy (OVX). The latter paradigm allows for the examination of a particular hormone of interest that can be administered to the animal in the absence of other ovarian hormones. The disadvantage is that the timecourse of hormonal blood levels in hormone-replaced animals does not exactly match normally cycling animals [63], and results may not generalize to the naturally occurring condition. For convenience, the term estrogen will be used in the following discussion when referring to both endogenous estrogen and exogenously-administered estrogen compounds (e.g. estradiol benzoate, 17β-estradiol). Table 2 is a summary of studies on ovarian hormonal influences during different phases of addiction.

Table 2
Summary of rodent studies examining effects of ovarian hormones on drug self-administration

Drug	Phase	General finding	Citation[a]
Cocaine	Acquisition	OVX+E>OVX−E	[64]
		Intact=OVX	[20]
	Maintenance	intact −E<intact FR 1	[65]
		OVX<intact FR 1	[66]
		OVX+E=OVX−E FR 1	[66]
		F estrus>BPs (PR)	[26]
		OVX+E=OVX−E FR 1	[67]
		OVX+E=OVX−E BPs (PR)	[67]
		F estrus>dysregulation	[9]
		OVX+E=OVX−E FR 5	[20]
	Relapse	OVX+E>OVX−E reinstatement	[69]
Heroin	Acquisition	OVX+E=OVX−E	[32]
		OVX+E<OVX −E rate	[70]
	Maintenance	OVX+E=OVX−E BPs (PR)	[32]
		OVX+E>OVX−E FR 1	[70]

[a] Citations listed are representative references discussed in the review.

3.1. Stimulants

3.1.1. Acquisition

There is a limited amount of research that has focused on the effects of ovarian hormones on the acquisition of drug self-administration. Lynch and coworkers [64] examined the role of estrogen in the acquisition of a low dose (0.2 mg/kg) of i.v. self-administered cocaine in female rats. The data from this study revealed that a greater percentage of intact, sham-operated female rats treated with vehicle and OVX female rats treated with estrogen acquired i.v. cocaine self-administration compared to female rats with estrogen surgically removed by OVX, or chemically blocked by the estrogen antagonist tamoxifen [64]. Conversely, Caine and coworkers [20] found no effect of OVX on the acquisition of a higher dose of i.v. self-administered cocaine (1.0 mg/kg) in female rats; however, mean rates of cocaine intake during the 5 days immediately preceding acquisition were significantly lower in OVX females compared with intact females.

3.1.2. Maintenance

Regarding maintenance of drug self-administration, Dalton and others [65] reported that treatment with the dopamine antagonist haloperidol, which has been demonstrated to increase the self-administration of cocaine in rodents, caused a significantly larger increase in cocaine self-administration in female rats than in males. It was also reported in the same study that treatment with the estrogen antagonist, tamoxifen, resulted in an attenuation of this effect in female rats [65]. Additionally, OVX reduced haloperidol's enhancement of cocaine self-administration, but these effects were not reversed when the same rats were given a number of estrogen treatments [66]. Grimm and See [67] reported that estrogen replacement in OVX female rats did not affect the maintenance of cocaine self-administration under an FR 1 schedule of reinforcement. Additionally, under an FR 5 schedule, cocaine dose–response curves were nearly identical in females before and after OVX, and in OVX females before and after estrogen replacement [20].

Roberts and coworkers [26] used a PR schedule of reinforcement to examine influences of ovarian hormones on the maintenance of cocaine self-administration in rats. They found that female rats reached higher BPs during the estrus phase (estrogen begins to rapidly decline from its peak level in proestrus) of their estrous cycle than during other stages of the cycle. Hecht and coworkers [68] also reported that female rats exhibited the highest BPs for cocaine during estrus. However, no influence of estrogen replacement in OVX female rats on cocaine-maintained responding under a PR schedule was reported in another study [67]. In fact, cocaine self-administration under a PR schedule was decreased on the day of, and 2 days following estrogen treatment in OVX females in this study [67].

3.1.3. Regulation/disregulation

In one study, the effects of ovarian hormones on the regulation and dysregulation of cocaine self-administration were examined [9]. In this study an adjusting dose self-selection procedure was used, and showed that female rats showed that the greatest dysregulation of cocaine self-administration and escalation in drug intake during the estrus phase of their estrous cycle. During the estrus phase female rats consumed nearly double the amount of cocaine (mg/kg) per day than the amount they consumed during other estrous phases [9].

3.1.4. Reinstatement

The effect of ovarian hormones on relapse to drug-seeking behaviors has not yet been reported in humans or animals. However, preliminary data revealed that following extinction of cocaine self-administration, priming injections of cocaine induced greater levels of responding on the cocaine-associated lever in SH + VEH and OVX + EB female rats compared to OVX + VEH female rats [69]. Therefore, estrogen may contribute to female rats' vulnerability to the reinstatement of cocaine self-administration following a period of cocaine abstinence [69].

3.2. Opioids

3.2.1. Acquisition

In an earlier study no influence of ovarian hormones on the acquisition of i.v. self-administered heroin in female rats was reported when multiple drug doses (0.00625, 0.012, 0.025 and 0.05 mg/kg) and relatively long self-administration sessions (12-h/day) were used [32]. However, in a more recent study the influence of estrogen on the acquisition of a single low dose (0.0075 mg/kg) of i.v. self-administered heroin was examined in female rats and OVX female rats treated daily with estrogen or vehicle, and the estrogen-treated rats acquired self-administration at a faster rate than vehicle-treated rats [70].

3.2.2. Maintenance

Stewart and coworkers [32] used a PR schedule of reinforcement to investigate the effects of ovarian hormones on BPs reached during heroin self-administration between OVX female rats and OVX female rats treated with estrogen. The results showed no significant influence of ovarian hormones on heroin-maintained responding [32]. Similarly, data from our laboratory revealed no effect of estrogen replacement in OVX female rats on BPs (highest ratio of response requirements completed to obtain one reinforcer) under a PR schedule for heroin self-administration [71]. However, data from another study revealed that OVX rats treated with estrogen responded for significantly more heroin under an FR 1 schedule of reinforcement during a 5-day maintenance period compared with OVX rats treated with vehicle [70].

3.3. Summary

The influence of ovarian hormones on drug self-administration in female rats is similar to that seen when examining sex differences. Specifically, it appears as if conditions that employ low doses of stimulants [64] and relatively challenging behavioral schedules [26] reveal the effects of ovarian hormones during transition states of drug addiction (e.g. acquisition, controlled to uncontrolled intake, relapse). Also, as seen with sex differences, the influence of ovarian hormones on the self-administration of non-stimulant drugs (e.g. opioids, ethanol, other drugs) is less consistent. Further studies are needed to examine the influence of female ovarian hormones on drug self-administration in animals. Additionally, although there is a fairly large body of literature investigating hormonal effects on drug abuse in rodents, there are very few studies that have investigated the influence of the menstrual cycle and female ovarian hormones in nonhuman primates. The information that would be obtained from studies in nonhuman primates will be important for taking the knowledge gained from this area of research and implementing it when designing prevention and treatment strategies for human drug abusers.

4. Neuropharmacological systems that are important in drug reinforcement

In order to better understand how an organism's sex and gonadal hormones influence the mechanisms of drug action, it is important to consider pharmacokinetic factors such as absorption, metabolism, and elimination of drugs [72]. Neurotransmission also plays a critical role in the mechanisms of action of drugs, and there is substantial evidence indicating sex differences in neurotransmission in brain regions thought to be important in drug abuse [73]. This evidence is important to consider when examining sex differences in the actions of drugs in the central nervous system. This section will give a broad overview of sex differences and ovarian hormonal influences on the pharmacokinetics of drugs of abuse. It is beyond the scope of this review to discuss all of the species differences in pharmacokinetics, but it is important to point out that males and females do differ in some pharmacokinetic responses to certain drugs of abuse, and that ovarian hormones may contribute to these differences. We will also discuss sex differences and ovarian hormonal influences in the neurotransmission associated with abused drugs. It should be noted that the following information was not gained from studies examining drug self-administration.

4.1. Sex differences

4.1.1. Pharmacokinetics

It is well known that there are differences between male and female humans and animals regarding body composition. Males typically weigh more and have a higher muscle to fat ratio than females; thus, males have a proportionally greater vascular capacity because fat is not vascularized. This can affect a number of pharmacokinetic parameters of drugs [74]. For example, due to the lack of vascular capacity in fat tissue, females have a decreased ability to absorb drugs such as alcohol and the same volume of alcohol is more diluted in the bloodstream of males than in females of comparable weight [75]. Therefore, the same amount of alcohol will often lead to elevated concentrations of alcohol in the bloodstream of females compared to males [76]. Females' higher percentage of body fat can also increase the duration of action of lipophilic drugs (e.g. PCP, marijuana) that are absorbed and stored in fat and slowly released into the blood. These differences typically have only a small effect on the pharmacokinetic profile of drugs; thus, sex differences in drug effects can be attributed to other factors.

One factor that has been examined in regard to sex differences in pharmacokinetics is hepatic metabolism. It has been reported that drugs metabolized in the liver via oxidative metabolism by the isozyme CYP3A4 [77–79] are eliminated faster by women than men. In contrast, drugs eliminated via oxidative metabolism by the isozymes CYP2C19 [80], CYP1A2 [81,82] and dihydrouracil dehydrogenase [83,84] may be eliminated faster in men. The glucuronidation activity involved in drug metabolism has also been indicated to be higher in males than females [74].

Other pharmacokinetic factors that may contribute to sex differences in the mechanisms of drug action include renal elimination, protein binding, and distribution. Mendelson and coworkers [85] reported that there were no differences in male and female humans regarding cocaine pharmacokinetics. Specifically, peak plasma levels, elimination half-life, and cardiovascular effects of i.v. administered cocaine were similar in men and women [85]. Conversely, there are sex differences in the metabolism of benzodiazepines (e.g. chlordiazepoxide and diazepam), which are metabolized primarily through microsomal oxidative pathways. These drugs maintain a longer half-life in females compared to males [86]. Additionally, females have a greater volume of distribution and higher total clearance for diazepam than males [87]. The excretion of oxazepam and temazepam, which are both eliminated almost entirely by conjugation, is greater in males compared to females since conjugation capacity is greater in males than females [86]. Finally, Green and others [88] reported that intact female cynomolgus monkeys had faster rates of ethanol elimination than males; however, there was no effect of menstrual cycle on the females' blood ethanol concentration or elimination, and there were no sex differences in the highest blood ethanol concentration measured 60 min after intragastric administration of 1 g/kg ethanol.

4.1.2. Neurotransmission

One commonality among drugs of abuse is that they all either directly or indirectly increase dopamine levels in

the striatum (e.g. caudate/putamen, nucleus accumbens) [89], and sex differences in dopaminergic neurotransmission in the striatum have been examined in several studies. In most studies, where the effects of psychostimulant-induced dopamine release were examined, female rats tended to display a greater dopaminergic response than males following the administration of these drugs. For example, Becker and Ramirez [90] used rat striatal tissue fragments in vitro to investigate sex differences in amphetamine-stimulated dopamine release and amphetamine-stimulated dopamine release was greater in females than males in this tissue. Similar results are seen for non-drug stimulation of dopamine release. For example, using fast cyclic voltammetry, Walker and coworkers [91] reported sex differences in dopaminergic neurotransmission in the striatum. Specifically, in vivo and in vitro data revealed that dopamine release and uptake rates were enhanced in the caudate nucleus of female rats compared to males, and that in vivo dopamine release was greater in females over a range of stimulation current intensities [91]. Differences in dopamine uptake rates may reflect differences in dopamine transmitter number or affinity, and sex differences in rat striatal dopamine uptake sites have been reported. For example, one study revealed that density of striatal dopamine uptake sites was higher in female than in male rats, suggesting that the activity of psychoactive drugs that act on neuronal dopamine uptake sites may differ according to an organism's sex [92]. Notably, increased dopamine concentrations in females compared to males have also been shown in other brain areas, including the medulla, pons, mid brain, thalamus and hypothalamus [93], suggesting that multiple brain regions may potentially contribute to sex differences in drug effects. Additionally, sex differences persist in the absence of hormones. Specifically, dopamine functioning between castrated (CAST) male and OVX female rats was significantly different [94–96].

4.2. Ovarian hormonal effects

4.2.1. Pharmacokinetics

Ovarian hormones affect pharmacokinetic properties of a variety of drugs. Several studies in humans have revealed that changes in the menstrual cycle are related to differential absorption and bioavailability of certain drugs. For example, gastric emptying is slower during the luteal phase of the menstrual cycle when progesterone levels are high and estrogen levels are moderate to low, compared to the follicular phase when progesterone levels are low and estrogen levels rise to their highest levels [74]. In fact, Wald and coworkers [97] reported that gastrointestinal transit time from mouth to cecum was prolonged by approximately 29% during the luteal phase compared to the follicular phase, potentially allowing for greater drug absorption.

Some females have reported sensitivity to menstrual effects that may influence the distribution of drugs (e.g. sodium retention, water content and urinary volume); however, these effects do not appear to occur in most females. Therefore, studies investigating the effect of ovarian hormones on drug distribution have not revealed significant changes during the menstrual cycle. Mendelson and colleagues [85] reported that aspects of cocaine pharmacokinetics (e.g. peak plasma levels, elimination half-life and area under the curve) did not differ in women during the follicular phase compared to the mid luteal phase of their menstrual cycles. However, Lammers and others [98] reviewed a number of studies that examined effects of menstrual cycle phase on alcohol pharmacokinetics, and the evidence suggested that the elimination time of alcohol was increased during the luteal phase compared to other phases of the cycle. The research is limited regarding the effects of ovarian hormones on pharmacokinetic properties of drugs; therefore, additional work is needed to determine if ovarian hormones are involved in this aspect of drug action.

4.2.2. Neurotransmission

The effects of ovarian hormones on regulation of neuronal activity (e.g. neurotransmission) have been described [99]. There is evidence that both estrogen and progesterone have effects on the mesocorticolimbic dopaminergic systems, a system believed to be important for the reinforcing effects of drugs [89]. However, the majority of research on ovarian hormonal mechanisms of action in this system has focused on the effects of estrogen. It has been proposed that estrogen enhances behavioral and neurochemical responses to psychomotor stimulants through induction of rapid changes in neuronal excitability and that this is achieved by estrogen's actions on membrane receptors located on intrinsic striatal neurons and dopamine terminals [73]. Estrogen's effects on intrinsic striatal GABAergic neurons produces decreased firing of recurrent collaterals that synapse on $GABA_B$ receptors found on dopamine terminals. This subsequently decreases $GABA_B$ receptor stimulation, which enhances stimulated dopamine release. Estrogen also downregulates D_2 dopamine autoreceptors which results in enhanced dopamine release. Studies exploring the effects of progesterone on mechanisms of action in the dopaminergic system are limited; however, Becker [73] reported that progesterone enhanced dopamine release in striatal tissue from estrogen-primed OVX female rats. This effect of progesterone was not seen without estrogen priming. It has been suggested that progesterone may actually induce inhibitory effects on the dopaminergic system [73].

Peris and coworkers [100] investigated the influence of ovarian hormones on the behavioral effects of repeated cocaine exposure and subsequent amphetamine-stimulated striatal [^{3}H]dopamine release. The authors exposed OVX female rats (treated with estrogen, progesterone, or estrogen plus progesterone) to repeated cocaine injections and subsequently injected the animals with amphetamine to determine the effects of this drug on in vitro striatal

[^{3}H]dopamine release. The results from this study indicated that OVX female rats treated with estrogen had the greatest amount of striatal [^{3}H]dopamine release following injections of amphetamine compared to OVX females treated with only progesterone, or progesterone plus estrogen [100]. In another study, nicotine-evoked dopamine release was increased in estrogen treated OVX female rats and decreased in estrogen treated CAST males [101]. These data support the hypothesis that dopamine release may be an estrogen-modulated, neurochemical substrate of repeated psychostimulant exposure.

Thompson and Moss [102] also investigated estrogen's ability to modulate mesolimbic dopamine release using in vivo voltammetry. The results showed that OVX female rats primed with injections of subcutaneous (s.c.) estrogen exhibited a decrease in potassium-stimulated dopamine release in the nucleus accumbens. This decrease was accompanied by a significant increase in dopamine reuptake and clearance times, which allowed dopamine to remain available for a longer period of time in the extracellular space. Additionally, direct infusions of estrogen into the nucleus accumbens produced initial increases (2 min after infusion) in potassium-stimulated dopamine release. Although there was reduction in this release after 15 min, the dopamine levels were still significantly higher than in control animals that received vehicle injections [102]. Thompson [103] investigated estrogen's effect on dopamine uptake and clearance via in vivo voltammetry after an injection of dopamine into the nucleus accumbens. They found that OVX plus estrogen rats vs. OVX rats had a significantly reduced rate of dopamine uptake and a significant increase in clearance time. These data suggest that estrogen can modulate aspects of dopaminergic functioning in the mesolimbic region of the brain.

Morissette and Di Paolo [92] investigated the effect of the estrous cycle on striatal dopamine uptake in female rats. The authors examined striatal dopamine uptake sites by labeling the sites with [^{3}H]GBR-12935, which has a high affinity and selectivity for the dopamine uptake complex. The results revealed that striatal [^{3}H]GBR-12935 binding density peaked in females during the morning of proestrus (when estrogen levels are high). Additionally, the density of [^{3}H]GBR-12935 striatal binding sites was lower in OVX rats compared to intact female rats. Therefore, striatal dopamine uptake site density fluctuates during the female estrous cycle, and peaks when levels of estrogen are highest [92].

Estrogen also alters dopamine receptor gene transcription. Lee and Mouradian [104] used transient cotransfection experiments to examine the effects of estrogen, progesterone, and glucocorticoid receptors on the regulation of D_{1A} dopamine receptor gene transcription. The results showed that following estrogen treatment there was a 1.7-fold induction of the D_{1A} gene. However, treatment with either progesterone or a glucocorticoid failed to induce any transcriptional regulation of the D_{1A} gene. The authors suggest that these results provide a basis for estrogen-induced up-regulation of D_{1A} gene transcription, and this up-regulation provides a mechanism for modulation of central dopaminergic functions by estrogen [104].

Although sex differences and ovarian hormonal influences on the pharmacokinetics of drugs of abuse are relatively unclear, it is apparent that sex differences occur in the neurotransmission of dopaminergic drugs of abuse. These sex differences appear to be attributable to estrogen's influence on dopaminergic responses to drugs of abuse, specifically stimulants. Further work needs to be conducted in order to determine the exact mechanisms by which estrogen contributes to sex differences in dopaminergic neurotransmission and to determine if sex differences exist in the neurotransmission of other abused drugs.

5. Sex differences in treatments for drug abuse

5.1. Pharmacotherapies

The research that has demonstrated sex differences in various phases of drug abuse has recently been extended to examine the question of whether there are sex differences in the treatment of drug abuse. Initial work with animal models indicates that females may be more preferentially responsive to treatment drugs than males. For example, Campbell and coworkers [11] reported that female rats were more responsive to the treatment effects of baclofen, a gamma-aminobutyrate B ($GABA_B$) agonist. The baclofen-pretreated female rats acquired cocaine self-administration at a significantly slower rate compared to males, and baclofen significantly reduced the percentage of female rats in the group that acquired cocaine self-administration compared to males. Their control condition showed that female rats treated with vehicle acquired cocaine self-administration at a faster rate than males treated with vehicle [11]. In another study ketoconazole, an inhibitor of corticosterone synthesis, significantly reduced food-restriction induced increases in i.v. heroin self-administration in female rats compared to males and that effect was reversed by coadministration of corticosterone [33]. In another study, the mu-opioid receptor antagonist CTOP reduced alcohol drinking in both male and female alcohol-preferring rats. The delta-opioid receptor antagonist ICI 174,865 had no effect on alcohol drinking in males, but it produced hind limb dysfunction and barrel rolling in more than half of the females [105].

Similar sex differences in treatments for drug abuse have been reported in rhesus monkeys. Male and female monkeys orally self-administered similar amounts of PCP (mg/kg) under an FR schedule, and low doses of bremazocine, a kappa-opioid receptor agonist, decreased the consumption of PCP significantly more in females than males [13]. These results indicate that certain pharmacological treatments are more effective in reducing the self-administration of certain

drugs of abuse in female vs. male animals. However, more preclinical research is needed to determine the extent of these effects.

5.2. Behavioral therapies-nondrug alternative reinforcers

Concurrent access to nondrug alternative reinforcers generally reduces drug self-administration [106]. For example, saccharin reduced the self-administration of PCP in male rhesus monkeys [106], and this varied as a function of the magnitude of the reinforcer (dose) and the cost (FR value) of the self-administered drug [107]. Furthermore, the combination of oral saccharin access and a pretreatment injection of buprenorphine, a partial mu-agonist, decreased the self-administration of PCP [108] to a greater extent than either treatment alone. Generally, the information gained from animal models indicates that a combination of nondrug alternative reinforcers and pharmacotherapies in addition to a high unit price (responses/mg) for the drug is the optimal treatment strategy to reduce drug intake [18]. A high unit price can be achieved by using either a high response requirement (FR) or a low dose of the self-administered drug.

Research examining the effectiveness of access to nondrug reinforcers has generally been conducted in males, but recently investigators have begun to examine sex differences in the effectiveness of these behavioral strategies. In animal studies, Cosgrove and coworkers [12] investigated the effect of a nondrug activity, wheel running, on i.v. cocaine self-administration in male and female rats. Wheel-running decreased i.v. cocaine intake to a significantly greater extent in females vs. males. Furthermore, wheel-running and cocaine self-administration were substitutable and interacted as reinforcers to a greater extent in female vs. male rats [12]. It has also been reported that saccharin functioned as a nondrug alternative reinforcer and reduced oral self-administration of PCP in both female and male rhesus monkeys [14]. However, saccharin access suppressed PCP consumption to a greater extent in female monkeys vs. male monkeys at low unit prices (FR values), while differences at higher FR values were obscured by a floor effect [14]. Overall, the results of several preclinical studies suggest that females respond more than males to the suppressant effects of nondrug alternative reinforcers and other behavioral treatments.

6. Future directions

There are many reports of sex differences in animal models of drug self-administration. It is apparent that an organism's sex influences the behaviors induced by drugs and drug-seeking behavior during all phases of drug abuse. Although sex differences in the mechanisms of drug action remain unclear, it is generally accepted that ovarian hormones play a major role in the differences reported in drug abuse between males and females. In particular, estrogen appears to modulate certain mechanisms of dopaminergic drug action. However, estrogen's interaction with drugs that act directly on other neurotransmitter systems is not well established. Future research using animal models of drug self-administration that examines the above factors may allow for the development of safe and effective sex-specific pharmacotherapies for drug addiction in humans. The development of pharmacotherapies that account for hormonal differences between sexes and ovarian hormonal fluctuations in women may also be possible. In conclusion, the recent trend in drug abuse research to include sex and hormonal status as independent variables will further our knowledge concerning factors that contribute to drug abuse and expand the generality of the results.

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