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REVIEW

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Biological basis of sex differences in drug abuse: preclinical and clinical studies

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Abstract The recent focus on drug abuse in women has brought attention to numerous differences between women and men. In this review, we discuss both preclinical and clinical findings of sex differences in drug abuse as well as mechanisms that may underlie these differences. Recent evidence suggests that the progression to dependence and abuse may differ between women and men; thus, different prevention and treatment strategies may be required. Similar sex differences in drug sensitivity and self-administration have been reported in laboratory animal studies. Females appear to be more vulnerable than males to the reinforcing effects of psychostimulants, opiates, and nicotine during many phases of the addiction process (e.g. acquisition, maintenance, dysregulation-escalation, relapse). Male and female animals differ in their behavioral, neurological, and pharmacological responses to drugs. Although the role of sex in the mechanisms of drug action remains unclear, preclinical and clinical studies indicate that ovarian hormones, particularly estrogen, play a role in producing sex differences in drug abuse. Future research is necessary to provide information on how to design more effective drug abuse treatment programs and resources that are sex specific.

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Introduction

Traditionally, drug abuse was considered to be primarily a problem specific to men. Thus, most drug abuse research has focused on the study of males. The recent focus on drug abuse in women has brought attention to numerous sex differences. Evidence generated thus far indicates that the biological response, long-term effects, and the causes and correlates of drug abuse may differ between women and men. In this review, we will discuss both preclinical and clinical findings of sex differences in drug abuse as well as mechanisms that may underlie these differences. Although very few studies have investigated the effect of pharmacological and environmental treatments in both males and females, we will explore some preliminary data regarding treatment outcome by sex.

Clinical reports of sex differences

In this section we briefly review some of the findings commonly reported on sex differences in epidemiology, biological response, patterns of use, progression, and health consequences. One major difference between women and men relating to drug abuse is revealed through epidemiological data. For instance, adult men are more likely than adult women to be current illicit substance users (7.7% versus 5.0%; except prescription medications), alcohol users (53.6% versus 40.2%), and tobacco users (35.2% versus 23.9%; SAMHSA 2001). Additionally, men are 2–3 times more likely than women to have a drug abuse/dependence disorder, and they are approximately 4 times as likely to have an alcohol use disorder (Brady and Randall 1999). Notably, when prevalence rates are compared among adolescents, the gender differential disappears. An equal number of adolescent males and females are current illicit drug

Table 1 Summary of human studies on sex and ovarian hormonal influences on drug abuse[a]. ↑ small, ↑↑ moderate, and ↑↑↑ large effects

Dependent measure/phase	Drug	Finding	Reference
Subjective effects	Cocaine	Women ↑↑ nervousness	Kosten et al. (1996)
		Women ↓↓ euphoria and dysphoria	Lucas et al. (1996)
		↑↑ high during follicular	Sofuoglu et al. (1999), Evans et al. (2002)
	Amphetamine	↑↑↑ euphoria and high during follicular	Justice and de Wit (1999)
		↑ pleasant stimulation with estrogen	Justice and de Wit (2000b)
	Nicotine	Women ↓ discrimination	Perkins (1999)
		↑↑ withdrawal during luteal	Allen et al. (2000)
	Alcohol	Women ↑ BAL	Mumenthaler et al. (1999)
		Limited ↑ during luteal (Effect may be limited to women with premenstrual dysphoria)	Mello et al. (1990)
Levels/patterns of use	Cocaine	No sex difference in total levels	Kosten et al. (1996)
		Women ↓ abstinence	Kosten et al. (1996)
	Nicotine	No sex or menstrual cycle effect on total levels	Perkins (2001)
		Women ↓ nicotine regulation	Perkins et al. (1992)
		Women ↓ abstinence	Perkins et al. (1999)
	Alcohol	Women ↓↓↓ levels of intake	Crawford and Ryder (1986)
		Limited ↑ during luteal phase	Mello et al. (1990)
	Opiates	No sex difference in total levels	Hser et al. (1987)
		No sex difference in patterns of use	Hser et al. (1987)
Relapse	Cocaine	Women ↑ cue reactivity	Robbins et al. (1999)
		Women ↑↑↑ craving during abstinence	Elman et al. (2001)
	Nicotine	Women ↑ non-nicotine reactivity	Perkins et al. (2001)
		No sex difference alcohol-induced reactivity	Rubonis et al. (1994)
	Alcohol	Women ↑↑ negative mood-induced craving	Rubonis et al. (1994)

[a] Citations listed are examples of relevant references

users (9.8% and 9.5%, respectively), and they have comparable rates of alcohol use (16.2% and 16.5%). Adolescent females have slightly higher rates of cigarette use (26.9% versus 23.1%), and nonmedical prescription drug use compared to males (3.3% versus 2.7%; SAMHSA 2001). Thus, the gender gap seems to be narrowing. However, consistent with adult populations, adolescent males report higher rates of binge and heavy alcohol use compared to adolescent females (SAMHSA 2001).

Women and men differ in their biological response to drugs (see Table 1). Results from studies investigating the effects of alcohol in women and men suggest that women are more sensitive than men to the physiological effects of alcohol. For example, following similar doses of alcohol, women achieve higher blood alcohol concentrations, and report feeling more intoxicated than men (Mumenthaler et al. 1999). Results from studies comparing intranasal cocaine users, indicate that women report greater "nervousness" than men (Kosten et al. 1996), but they take longer to detect the subjective effects of cocaine, and report less euphoria and dysphoria compared to men (Lucas et al. 1996). Similar results have been reported following a single dose of smoked cocaine (Sofuoglu et al. 1999) and following repeated "binge" smoked cocaine (Evans et al. 1999). Sex differences have also been reported in response to nicotine. For example, female smokers show less sensitivity than male smokers to the discriminative stimulus effects of nicotine (for review see Perkins 1999). However, in women positive mood is increased to a greater extent after smoking, and women show a greater decline in positive mood during smoking abstinence than men (Perkins 2001).

Women and men also differ in patterns of alcohol and cigarette use. For example, retrospective reports from alcoholics reveal that women consume lower levels, and are less likely than men to use daily or to engage in binge patterns of use (Orford and Keddie 1985; Crawford and Ryder 1986; SAMHSA 2001). Women and men also differ on patterns of cigarette smoking. Specifically, women show less compensation than men in their smoking behavior following either nicotine pretreatment or a change in nicotine dose suggesting that the interoceptive nicotine cues are less important in regulating smoking (Perkins et al. 1992). However, women consistently show shorter or less frequent abstinence periods compared to men (Perkins et al. 1999). More similarities than differences have been reported for patterns of cocaine and heroin use. For example, Kosten et al. (1996) reported that women and men spent an equal amount of money on cocaine, and both groups used for approximately the same number of days/month. One difference they found was that women reported shorter abstinence periods than men. In a study comparing narcotic use in women and men in a methadone maintenance program, Hser et al. (1987) reported that time spent using, amount used, abstinence periods, and number of relapses did not differ by sex.

The course or progression to dependence may differ between men and women. It has often been suggested in

the alcohol literature that women progress through the landmark stages to dependence at a faster rate than men (Orford and Keddie 1985; Lex 1991; Brady and Randall 1999; Randall et al. 1999). This has been termed telescoping, and it describes a shorter time course for the development of medical consequences and behavioral/psychological factors characteristic of an alcohol dependence disorder. Similar suggestions have been proposed for a variety of other drugs (Anglin et al. 1987; Hser et al. 1987; Griffin 1989; Kosten et al. 1993; Westermeyer and Boedicker 2000). For example, Westermeyer and Boedicker (2000) compared women and men on patterns of tobacco, caffeine, alcohol, cannabis, opiates, sedatives, cocaine, inhalants, amphetamine, hallucinogens, and phencyclidine (PCP) use and found that women used each drug, except cocaine, for a shorter time period compared to men. However, rates of dependence were similar between women and men suggesting that women take less time to progress to dependence than men.

Both the long-term and short-term effects of drugs may impose differential consequences on the health of women and men, and in many cases, women appear to be more sensitive to the adverse health effects of drugs than men. For example, despite lower levels of alcohol intake, and shorter periods of drinking, women have more severe medical consequences such as liver cirrhosis (Jarque-Lopez et al. 2001). Women are also at greater risk of smoking-related health problems such as myocardial infarction and lung cancer (for a review see Perkins 2001). In a study comparing male and female crack users, Dudish et al. (1996) reported that women have more emergency room visits following crack use than do men. Additionally, women using drugs intravenously are at a higher risk of acquiring HIV compared to men (Center for Disease Control and Prevention 1997). Women drug users also have medical risks not experienced by men. For example, women who use drugs during pregnancy place themselves and their offspring at risk for serious disorders such as fetal alcohol syndrome (SAMHSA 1996). Thus, prevention and treatment programs targeted toward women could have an important impact on the prevalence of drug-related health problems in our society.

Women and men differ in comorbid psychiatric diagnoses. Affective and anxiety disorders are higher in women who are dependent on alcohol, opiates, and cigarettes compared to men (e.g. Cornelius et al. 1995; Brooner et al. 1997; Borrelli et al. 1999), whereas men typically have higher rates of antisocial personality disorder (Cornelius et al. 1995). Equal rates of affective disorders have been reported for cocaine users, although women have higher rates of anxiety disorders (Lundy et al. 1995; McCance-Katz 1999). The presence of a comorbid psychiatric disorder can affect the course, severity, and treatment outcome of drug abuse. For instance, depression, depressive symptoms, and negative mood, appear to be associated with a lower likelihood of drug abstinence and a greater likelihood of relapse to drug use, particularly for alcohol and cigarette use (Connors et al. 1998; Borrelli et al. 1999). Thus, women may be at greater risk on several dimensions of drug abuse compared to men.

These sex differences in drug abuse may be due to sociocultural factors or to innate biological differences. For example, women experience more social disapproval for drug use (Beckman and Amaro 1986; Gomberg 1993; Reed and Mowbray 1999); thus, drug use is more stigmatized for women than it is for men. However, societal views about drug use in women are changing, and drug use in women is becoming more acceptable and less stigmatized (Nicolaides 1996). The question is, how will these changing views on drug use in women affect the number of women and the proportion of women to men who use and abuse drugs? There is some evidence to suggest that the sex difference in prevalence of drug use may be due to differences in drug use opportunity rather than vulnerability to drug use. Specifically, Van Etten et al. (1999) examined the occurrence of opportunity to use marijuana, cocaine, hallucinogens, and heroin among males and females beginning at age 12. They reported that although males were more likely to have had an opportunity to use each of these drugs, females were just as likely as males to use drugs once an opportunity had occurred. Sex differences in drug abuse may be due to different approaches to seeking medical treatment. We do know that women use the medical system to a greater extent than do men, and that women will see more health care providers in their lifetime than will men (Blume 1986, 1990). Thus, women may be more likely than men to seek treatment for drug abuse and may seek it earlier in the course of the disorder than males. Finally, the differences in drug abuse between women and men may be due to an innate biological sex difference. That is, there may be mechanistic, metabolic, or hormonal differences that cause women and men to respond differently to drugs. Animal models are useful in addressing some of these questions on the effect of sex in drug abuse.

Preclinical reports of sex differences

Animal models of drug abuse have been critical for guiding the development of prevention and treatment strategies used in clinical populations. The traditional animal model entails training an animal to self-administer a relatively high dose of a drug using fairly unrestricted access conditions [e.g. each response is reinforced under a fixed ratio (FR) 1 schedule] during short daily sessions (1–3 h). Under these conditions, most, if not all, animals rapidly acquire drug self-administration. Once levels of intake stabilize, the effect of pharmacological and environmental manipulations are examined on the stable maintenance levels of intake. While the traditional animal model has been extremely valuable for investigating the effects of various treatments, and for identifying variables related to the reinforcing effects of drugs, these conditions minimize intersubject variability, and they may not be

Table 2 Summary of animal studies on sex and ovarian hormonal influences on drug abuse[a]. ↑ small, ↑↑ moderate, and ↑↑↑ large effects

Dependent measure/phase	Drug	Finding	Reference
Behavioral response	Amphetamine	Female ↑↑↑	Camp et al. (1986)
		↑ estrous	Becker et al. (1982)
	Cocaine	Female ↑↑↑	Sell et al. (2000)
		Female + estrogen ↑↑↑	Sell et al. (2000)
		↑↑ estrous and proestrus	Sell et al. (2000)
Acquisition	Cocaine	Mixed results; females ↑↑↑ or no sex difference	Lynch and Carroll (1999)
			Haney et al. (1995)
		Females+estrogen ↑↑↑	Lynch et al. (2001)
	Methamphet-amine	Females ↑↑↑	Roth and Carroll (unpublished data)
	Nicotine	Females ↑	Donny et al. (2000)
	Alcohol	Mixed results; females ↓ or ↑ (may depend on species and/or access conditions)	Grant and Johanson (1988), Juarez et al. (1993)
	Heroin	Mixed results; females ↑↑ or no sex difference	Lynch and Carroll (1999)
			Stewart et al. (1996)
		Females+estrogen ↑	Roth et al. (2002)
	PCP	Females ↑	Carroll et al. (2000)
Levels/patterns of intake	Cocaine	No effect of sex or ovarian hormones on total intake	Lynch et al. (2000)
		Females ↑↑↑ break point	Roberts et al. (1989)
		↑↑↑ break point in estrus	Roberts et al. (1989)
		Females ↑ dysregulation	Lynch et al. (2000)
	Nicotine	No effect of sex or ovarian hormones on total intake	Donny et al. (2000)
		Females ↑ break point	Donny et al. (2000)
	Alcohol	Mixed results; females ↓ or ↑ or no sex difference (may depend on species and/or access conditions)	Vivian et al. (2001), Juaraz et al. (1993), Pakarinen et al. (1999)
		↑ during luteal phase	Mello et al. (1986)
	Heroin	No effect of sex or ovarian hormones on total intake or break point	Stewart et al. (1996)
Reinstatement responding	Cocaine	Females ↑↑↑	Lynch and Carroll (2000)
	Fentanyl	Females ↑↑	Klein et al. (1997)

[a] Citations listed are examples of relevant references

optimal for detecting individual differences (e.g. sex) in drug self-administration.

Most of the data that are available on sex differences in drug use have been obtained using traditional animal models (see Table 2). Results obtained for alcohol suggest that patterns of intake for male and female animals vary between different species. For example, results from studies in rats and vervet monkeys on total alcohol intake revealed that females self-administer greater levels of alcohol compared to males (Lancaster and Spiegel 1992; Juarez et al. 1993; Almeida et al. 1998; Juarez and Barrios de Tomasi 1999). In contrast, studies comparing male and female rhesus monkeys reveal that females are less likely than males to maintain consumption (Grant and Johanson 1988), but they self-administer similar levels of alcohol across a wide range of concentrations (Pakarinen et al. 1999; Vivian et al. 1999). These preclinical data are discrepant with data obtained with humans showing that men drink greater amounts of alcohol compared to women (Orford and Keddie 1985; Crawford and Ryder 1986). Results from one study comparing male and female rhesus monkeys under extended access conditions are analogous to those observed in humans. Specifically, Vivian et al. (2001) compared male and female rhesus monkeys on alcohol self-administration during daily 16- or 22-h sessions over a 9-month period. Under these conditions, individual differences in alcohol consumption emerged to reveal heavy, moderate, and light drinkers. Furthermore, consistent with findings reported in humans, a greater percentage of heavy drinkers were males, and males drank more alcohol (g/kg) on average than females. Taken together, these results show that sex differences in patterns of alcohol intake depend on species and environmental conditions.

Patterns of opiate intake have also been compared between male and female animals. For example, Lynch and Carroll (1999) compared male and female rats on heroin self-administration during 6-h daily sessions over a 5-day period and reported no sex differences in levels of intake. Similar findings have been reported for heroin self-administration during initial drug self-administration sessions (Stewart et al. 1996). In contrast, when male and female rodents are compared under either extended access conditions and/or over a long time period results have shown that female mice and rats consume greater levels of heroin (Carroll et al. 2001) and morphine (Alexander et al. 1978; Hadaway et al. 1979) compared to male mice and rats. These results suggest that sex differences in opiate intake may depend on access conditions and that they may become more apparent over time.

In studies using the traditional animal model for cocaine and nicotine self-administration, male and female do not differ in their rate of responding (Roberts et al. 1989; Haney et al. 1995; Lynch and Carroll 1999; Donny et al. 2000). However, sex differences emerge when levels of responding are examined under a progressive ratio (PR) schedule. With this procedure, the response requirement per infusion (ratio) escalates for each successive drug infusion within a daily session until responding ceases. The highest ratio completed (or break point) has been used as a measure of reinforcing efficacy or motivation to obtain the reinforcer, and it has been shown to be sensitive to changes in unit dose, genetic strain, and pharmacological manipulations (for review, see Arnold and Roberts 1997; Stafford et al. 1998). Roberts et al. (1989) used a PR schedule to compare male and female rats on cocaine-reinforced responding during a maintenance phase, and they reported that females reached break points that were considerably higher than those reached by males. These data suggest that females may be more sensitive than males to the reinforcing effects of cocaine. A recent report of intravenous cocaine self-administration under a PR schedule in rats selectively bred for low (LoS) and high (HiS) saccharin intake also indicated higher break points for cocaine self-administration in females compared to males in both the LoS and HiS groups (Carroll et al. 2002). Similar results have been reported for rats self-administering methamphetamine (Roth and Carroll, unpublished data), nicotine (Donny et al. 2000) and fentanyl (Klein et al. 1997). These results suggest that females are more motivated to self-administer cocaine, methamphetamine, nicotine, and fentanyl. These preclinical data may have implications for research conducted with human subjects; specifically, that negative findings for patterns of intake or total intake do not necessarily mean that sex differences are not relevant. Rather, negative findings may simply mean that more challenging behavioral schedules are required to reveal sex differences. In preclinical studies, the use of low doses is another procedural technique for revealing sex differences (Carroll et al. 2000, 2002) as well as other endogenous differences such as activity level (Mantsch et al. 2001) during acquisition and maintenance phases.

Modeling phases of drug addiction

Studying drug self-administration at the transition phases of drug addiction may also be a sensitive method for detecting sex differences. Animal models of the transition phases of acquisition, escalation, and relapse are crucial, since ethical considerations do not allow these processes to be thoroughly studied in the human laboratory. These phases include the transition from drug naive to drug experienced, the escalation from controlled use to uncontrolled, dysregulated, binge use, and the transition from drug abstinence to relapse. Each of these phases has been modeled in animals; however, males and females have been compared in only a few of these studies.

Acquisition

Human studies

In humans, the acquisition phase encompasses the transition from initial drug sampling to regular use. Clinical data suggest that a strong predictor of the development of

drug addiction is the individual's "vulnerability" to the reinforcing effects of drugs (Gawin 1989). Retrospective reports from drug users reveal that the response to initial drug exposure varies from highly positive to negative (Gawin 1989). It has been suggested that the initial response to a drug may predict the likelihood of continued use (Davidson et al. 1993); however, very few studies have examined the effect of sex on the initial response to drugs.

Animal studies

Consistent with the clinical findings, there is considerable variability in laboratory animals in propensity to self-administer drugs, and animal models of the acquisition phase have been developed to identify biological and behavioral factors underlying individual differences in vulnerability that may apply to prevention efforts in humans (for review, see Campbell and Carroll 2000). Drug naive animals are trained to self-administer drugs under conditions that produce relatively slow rates of acquisition (i.e. very low doses). In this situation, all of the animals are included in the analyses, whether or not they acquire self-administration, and the focus is on how rapidly this process takes place and what percentage of animals acquire drug-reinforced responding (e.g. Carroll and Lac 1993, 1997; 1998; Lynch and Carroll 1999; Campbell et al. 2002).

These models have been useful in addressing the question of sex differences to the reinforcing effects of drugs. Results from studies comparing males and females during the acquisition phase have revealed sex differences. Specifically, female rats acquired cocaine and heroin self-administration at a faster rate than male rats, and a greater percentage of female rats acquired cocaine self-administration than males (Lynch and Carroll 1999; Carroll et al. 2002). Similar results have been reported for rats self-administering methamphetamine (Roth and Carroll, unpublished data) and nicotine (Donny et al. 2000), rhesus monkeys self-administering PCP (Carroll et al. 2000), and vervet monkeys self-administering alcohol (Juarez et al. 1993). However, results from two studies with rats indicated that males and females did not differ during the acquisition phase (Haney et al. 1995; Stewart et al. 1996). In both of these studies, however, high doses of cocaine (Haney et al. 1995) and heroin (Stewart et al. 1996) were tested, and all animals acquired self-administration rapidly. In contrast, Grant and Johanson (1988) reported that male rhesus monkeys may be more sensitive to acquisition of alcohol self-administration. In this study, both drug-experienced and drug-naive male and female rhesus monkeys were compared on acquisition of oral alcohol self-administration following a sucrose conditioning procedure. They found that only male monkeys met the acquisition criterion; however, of the nine total animals tested only three monkeys acquired, and all of them had previous experience with drug self-administration.

The results of these acquisition studies indicate that sex differences may be obscured using conditions that produce rapid rates of acquisition (e.g. high dose, drug experienced animals, extended access to drug). Future studies are necessary to examine the conditions under which sex differences are revealed in the acquisition phase.

Escalation/dysregulation

Human studies

The clinical literature indicates that cocaine addiction begins with casual, recreational use, but progresses to uncontrolled and binge patterns of use, presumably due to motivational changes in drug-seeking behavior (Gawin 1991). Whether there are sex differences during the transition from controlled to uncontrolled drug use is not yet understood. A study by Westermeyer and Boedicker (2000) suggests that the course to dependence may differ between men and women in that women enter treatment programs after fewer years of drug use and take less time to become addicted to drugs after initial use than do men. These data suggest that in women there is an accelerated transition from casual, controlled use to uncontrolled, "binge" patterns of use. However, very few clinical or preclinical studies have investigated the transition from controlled, regulated use to uncontrolled, "binge" use, and even fewer have investigated sex differences during this transition.

Animal studies

Recently, several approaches have been used to model in animals the transition from controlled, regulated drug self-administration to uncontrolled, "binge" patterns of self-administration, or dysregulation (Wolffgramm and Heyne 1991; Fitch and Roberts 1993; Heyne 1996; Ahmed and Koob 1998, 1999; Heyne and Wolffgramm 1998; Deroche et al. 1999; Grimm et al. 2001; Mutschler et al. 2001; Tornatzky and Miczek 2000; Roberts et al. 2002). For example, Wolffgramm and Heyne (1991) developed an animal model of this transitional phase for oral alcohol self-administration in rats. Their procedure entails long-term ad libitum self-administration (1–2 months) followed by an extended drug abstinence period (4–9 months). Subsequently, rats are retested on self-administration behavior, and those animals that developed escalating patterns of intake prior to abstinence self-administered higher levels of intake compared to rats that did not show escalation. These investigators have subsequently developed models of opiate (Heyne 1996) and *d*-amphetamine (Heyne and Wolffgramm 1998) addiction using similar experimental conditions (for reviews see Wolffgramm and Heyne 1996; Wolffgramm et al. 2000).

Male and female animals have been compared in only one study of the transition from regulated to dysregulated

intake. Lynch and Carroll (2000) compared regulation of cocaine intake in rats using a two-lever drug self-administration procedure that allowed subjects to increase and decrease their dose of cocaine in discrete steps throughout each session (see also Lynch et al. 1998). Regulation was defined as a significant correlation between preceding dose size and mean interdose interval. Results showed while both males and females regulated their intake of cocaine, females regulated their intake less precisely than males showing more variability in the spacing of individual drug infusions over the course of 5-h self-administration sessions. These results suggest that females may be more vulnerable to developing erratic, binge-like patterns of cocaine intake than males. However, this study compared patterns of intake, but did not investigate motivational changes following abstinence from cocaine self-administration. Future studies are necessary to investigate this transitional phase in male and female animals.

Relapse

Human studies

In this review, relapse is defined as reinstatement of behavior that was previously reinforced by a drug. In humans, relapse refers to a transition from a period of drug abstinence to regular drug use. In both humans and animals, relapse can be precipitated by both internal and external cues; such as exposure to a priming dose of a drug or external cues such as places and drug-associated paraphernalia, respectively. The clinical literature suggests that men and women respond differently to internal and external drug stimuli. For example, internal drug cues modulate both maintenance and relapse to smoking in men; whereas, external drug cues are more salient for women (Perkins et al. 2001), a finding consistent with reports that nicotine has less influence on smoking behavior in women compared to men. The type of external cue that illicits cue reactivity (i.e. craving, heart rate) also varies between women and men. For example, Rubonis et al. (1994) reported that alcoholic women have greater urges to drink and smoke in response to negative mood induction, but do not differ from men following alcohol beverage cues. Similar results have been reported for cue reactivity among smokers (Niaura et al. 1998). In a study comparing levels of cocaine use reactivity, Robbins et al. (1999) reported that cues associated with cocaine use produced greater increases in craving in women compared to men. Few studies have examined sex differences in response to type of cue for other drugs.

Retrospective reports from addicts suggest that women and men may differ on relapse behaviors. For example, women report shorter cocaine abstinence periods than do men (Kosten et al. 1993), and during abstinence women report higher levels of craving and increased depressive symptomatology compared to men (Elman et al. 2001). Reasons for relapse to drug use may also differ between men and women; however, very few studies have investigated this possibility. There is some evidence to suggest that women are more likely than men to attribute relapse to a stressful event or to depression (Swan et al. 1988; Gritz et al. 1996; Snow and Anderson 2000). However, it is not clear whether women are more or less vulnerable than men to relapse, as there are studies to support both positions (e.g. Fortmann and Killen 1994; Fiorentine et al. 1997; Weiss et al. 1997).

Animal studies

Animal models of relapse have been developed (Gerber and Stretch 1975; de Wit and Stewart 1981; 1983; Shaham et al. 1994); however, very few studies have evaluated the effect of sex on relapse behavior. These animal models of relapse have focused predominantly on the role of internal stimuli on drug seeking behavior (for review, see Carroll and Comer 1996). The basic experimental design is to train animals to self-administer a drug to stable levels and replace the drug with vehicle (e.g. saline) allowing responding to extinguish. Relapse, or reinstatement of responding, is tested hours or preferably days later by administering a priming injection of the previously self-administered drug. Lynch and Carroll (2000) compared males and females on reinstatement of extinguished cocaine-reinforced responding. They found that both extinction and reinstatement responding were greater in female rats than in male rats, and it occurred after a lower priming dose of cocaine in females than in males. Similar findings have been reported for fentanyl self-administration (Klein et al. 1997). These data suggest that females are more vulnerable to the reinforcing effects of cocaine and fentanyl during the reinstatement phase. However, the investigation of sex differences in the reinstatement phase is an understudied area, and whether these results can be generalized to other drugs and other species needs to be determined. Additionally, the effects of external versus internal drug cues on reinstatement responding in males and females need to be explored. As with acquisition of drug taking, both individual differences (e.g. sex) and environmental factors determine which individuals will be protected or at risk for relapse to drug use.

Influence of ovarian hormones on responses to drugs

Human studies

Ovarian hormones play a role in the differences between males and females regarding responses to drugs of abuse. Figure 1a depicts the phases of the human menstrual cycle. The three phases that are typically studied in drug abuse research include the 1) follicular (estrogen levels are low at first and moderate later, and progesterone levels are low), 2) periovulatory (estrogen levels peak and then decline; progesterone levels begin to rise), and 3)

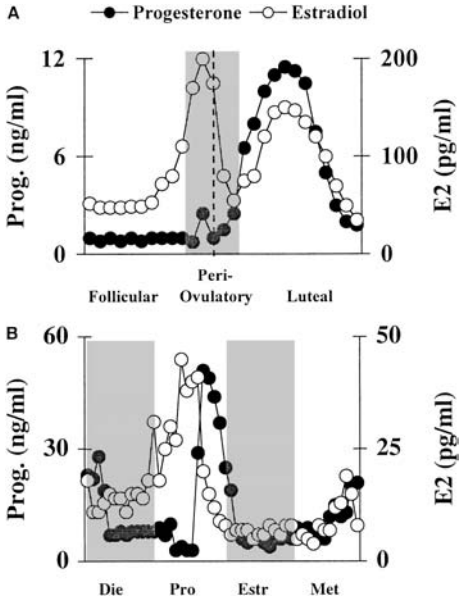

Fig. 1 **A** Changes in levels of estrogen and progesterone as a function of days from the *preovulatory* LH surge for the human menstrual cycle. The *shaded bar* separates the periovulatory phase from the follicular and luteal phases. Data were redrawn based on data presented by Mello and Mendelson (1997). **B** Changes in levels of estrogen and progesterone throughout the phases of the rat estrous cycle. The *shaded bars* separate the successive estrous cycle phases diestrus (*DIE*), proestrus (*PRO*), estrus (*ESTR*), and metestrus (*MET*) to identify the start and end of each phase. Data were redrawn from those presented by Freeman (1994)

luteal (estrogen levels are moderate and progesterone levels are high) phases (Lammers et al. 1995).

The effects of hormonal influences on responses to drugs of abuse in humans have been examined in several studies. Results from a series of studies have revealed that subjective responses to *d*-amphetamine vary across the menstrual cycle (Justice and deWit 1999, 2000a). The authors reported that several positive subjective effects of *d*-amphetamine such as euphoria, liking and wanting, and energy and intellectual efficiency were enhanced during the follicular phase relative to the luteal phase, and that these effects were positively correlated with estrogen levels (Justice and deWit 1999). They also suggested that the lack of enhanced *d*-amphetamine effects during the luteal phase may be due to progesterone's ability to mask effects of estrogen (Justice and de Wit 1999). The same authors also compared the subjective effects of *d*-amphetamine in women during the early and late follicular phase. It was reported that subjective responses to *d*-amphetamine were enhanced during the late (when estrogen is moderate) versus early (when estrogen is low) follicular phase. In a more recent study, Justice and de Wit (2000b) further explored the role of estrogen on the subjective effects of amphetamine by administering estradiol patches to women during the follicular phase of the menstrual cycle. Consistent with prior findings, they reported that estradiol increased positive subjective effects of *d*-amphetamine such as stimulation and decreased ratings of "want more". Additionally, they found that estradiol alone increased positive subjective effects that are associated with amphetamine use such as "feel high", and "pleasant stimulation". Therefore, it appears that estrogen played a role in modulating the subjective effects of amphetamine in humans. Similar results have been reported for the subjective effects of smoked cocaine. For example, women report higher ratings of "feel high" in the follicular phase compared to the luteal phase (Sofuoglu et al. 1999; Evans et al. 2002).

The subjective effects of alcohol have also been compared at different phases of the menstrual cycle in women. For example, Holdstock and deWit (2000) compared women in the early and late follicular and mid and late luteal phases on the subjective effects of alcohol and found no differences between the phases. However, the women tested in this study were light social drinkers without significant premenstrual dysphoria. Significant effects of menstrual cycle phase have been observed in studies that have included women with premenstrual dysphoria (Sutker et al. 1983; Harvey and Beckman 1985; Mello et al. 1990; Tate and Charette 1991). The subjective effects of alcohol as a function of menstrual cycle phase in alcoholic women is not well understood.

Studies investigating the subjective effects of nicotine or smoking as a function of menstrual cycle phase have been conducted mainly during an abstinence period (Allen et al. 2000; Perkins et al. 2000). For example, Allen et al. (2000) reported that premenstrual symptomatology and nicotine withdrawal symptoms were greatest during the late luteal phase, and that nicotine was effective in decreasing premenstrual pain and nicotine craving, particularly during this phase. Consistent with reports for alcohol, the subjective effects of smoking in women who were not trying to quit do not seem to vary across the menstrual cycle, except in women with premenstrual dysphoria (Perkins 2001). The subjective effects of opiate administration as a function of menstrual cycle phase have not yet been characterized.

Animal studies

Rodent studies have focused on behavioral responses to drugs as a function of ovarian hormone levels. Figure 1b shows that the rodent estrous cycle is divided into four phases: 1) proestrus (estrogen rises to highest levels and progesterone levels are low at the beginning and rapidly rise and descend toward the end), 2) estrus (estrogen and progesterone levels rapidly decline), 3) metestrus (estrogen levels are low and progesterone levels begin to rise), and 4) diestrus (estrogen levels are rising and progesterone levels decline; Freeman 1994).

Most of the studies investigating the behavioral effects of drugs across phases of the estrous cycle and following hormonal manipulations have been done with psychostimulants. For instance, it was reported that hyperactivity induced by cocaine was greatest in female rats during

proestrus (when estrogen levels peak) and estrus (when estrogen levels rapidly decline) (Sell et al. 2000). Sell et al. (2000) reported that ovariectomized (OVX) female rats treated with estrogen, or estrogen and progesterone showed enhanced behavioral responsiveness (e.g. horizontal and vertical locomotor activity) to cocaine when they were compared to OVX rats treated with progesterone alone or vehicle. Similarly, OVX female rats displayed attenuated amphetamine-induced behaviors, while estrogen treatment enhanced these behaviors in OVX female rats (Becker 1990).

Estrogen in female rats has been implicated in the enhancement of cocaine-induced behavioral sensitization, which is an increased behavioral response to a drug after repeated exposure to that drug (Peris et al. 1991). Specifically, OVX female rats treated with estrogen displayed a significantly greater degree of cocaine-induced behavioral sensitization compared to rats treated with progesterone alone or vehicle (Peris et al. 1991). The effects of estrogen on behavioral responses to stimulants are sexually dimorphic. For example, estrogen administered to male rats does not have the same effect on behavioral responses to psychostimulants as in female rats (Becker 1990; Castner et al. 1993). However, results from alcohol self-administration studies indicate that estrogen can produce effects in male rats (Hilakivi-Clarke 1995; Jaurez et al. 2002). For example, Hilakivi-Clarke (1995) reported that estrogen treatment stimulated alcohol consumption and alcohol-induced aggressive behavior in male mice.

In summary, in both humans and rodents, estrogen appears to play a role in the enhanced responsiveness of psychostimulants in females. When estrogen is present and relatively unopposed by progesterone (e.g. follicular phase), women experience an enhanced subjective experience to *d*-amphetamine and cocaine. In contrast, with alcohol and nicotine the greatest subjective effects are reported in the luteal phase, particularly in women with premenstrual dysphoria and during withdrawal. As these effects may correlate with dysphoric states, it might be hypothesized that elevated intakes of alcohol or nicotine may represent an attempt to self-medicate. In rodents, there is growing evidence that implicates estrogen as a major factor in females' enhanced behavioral responsiveness and sensitivity to psychostimulants. Future studies are necessary to investigate the effects of estrogen on other drugs of abuse. The following sections summarize the results of studies on the effects of gonadal hormones on drug self-administration during different phases of addiction.

Hormonal influences during acquisition

Animal studies

There is a limited amount of research that has focused on the effect of ovarian hormones on acquisition of drug self-administration. Lynch et al. (2001) examined the role of estrogen in the acquisition of cocaine self-administration through the use of estrogen replacement in OVX female rats and tamoxifen (antiestrogen) in intact female rats. Results revealed that chemical blockade or surgical removal of estrogen greatly reduced cocaine self-administration during acquisition compared to rats that had estrogen. Similar results have been reported for heroin self-administration (Roth et al. 2002). However, Stewart et al. (1996) did not find effects of ovarian hormones on acquisition of heroin self-administration in female rats. An effect may have been occluded in this study due to the high doses of heroin used during the acquisition portion of this experiment.

Hormonal influences during maintenance

Human studies

Few studies have examined hormonal influences on total intake of drugs in either humans or animals. However, the results that are available on total intake are similar to those reported for the subjective effects of drugs. For example, results comparing alcohol intake in women across menstrual cycle phase have revealed that intake is increased in the late luteal phase, particularly among women with premenstrual dysphoria (Mello et al. 1990). Although studies with nonhuman primates have reported similar findings of increased levels of alcohol intake (Mello et al. 1986) and alcohol discrimination (Grant et al. 1997) during the luteal phase, it is not clear if these results are restricted to women with premenstrual dysphoria. For example, when women with premenstrual dysphoria are excluded, no effect of menstrual cycle on total intake is observed (Holdstock and deWit 2000).

The human menstrual cycle may also influence nicotine intake; however, as with alcohol, this effect may be more pronounced in women with premenstrual dysphoria. Additionally, although self-reports indicate women alter their smoking behavior as a function of menstrual cycle phase, actual cotinine levels do not differ between phases in women with or without a history of depression suggesting that total intake is not affected by menstrual cycle phase (Pomerleau et al. 2000).

Animal studies

In general, results obtained for total intake across the estrous cycle of the rat have revealed no differences for cocaine (Roberts et al. 1989; Haney et al. 1995; Bowen et al. 2001; Lynch et al. 2001), heroin (Stewart et al. 1996), or nicotine (Donny et al. 2000). However, ovarian hormonal effects may have been occluded in these studies due to behavioral schedules of drug reinforcement that lead to ceiling effects (e.g. low FRs). More challenging behavioral schedules of reinforcement (e.g. PR) may be more sensitive to detecting effects of sex. Roberts et al. (1989) examined the effect of ovarian hormones on the

maintenance of cocaine self-administration in rats using an FR1 schedule of reinforcement, and there was no hormonal effect during the maintenance phase of drug self-administration. However, when the same authors used a PR schedule, significant sex differences were revealed; female rats reached higher break points during estrus compared to any other phase. Hecht et al. (1999) also reported that female rats exhibited the highest break points for cocaine self-administration during estrus. Thus, motivation to self-administer cocaine varies with the estrous cycle.

To date, there are no known reports on the influence of ovarian hormones on the relapse phase of drug addiction in either humans or animals. The investigation of how ovarian hormones influence this phase of drug addiction is necessary to determine whether females are more vulnerable to the reinstatement of drug-taking behavior at different periods throughout their reproductive cycle. However, it is important to note that the rodent estrous cycle is very different from the menstrual cycle in women, and whether the results obtained with rodents are applicable to women is not yet known. The rodent data predict that the reinforcing effects of drugs vary with levels of estrogen, a prediction that is consistent with the human data (e.g. Justice and de Wit 1999). The rodent data also suggest possible neurobiological mechanisms that underlie the hormonal effects on cocaine reinforcement (i.e. estrogen-dopamine interactions).

Effect of ovarian hormones on neurotransmission

Neurotransmission plays a critical role in the mechanisms of action of drugs, and there is evidence from both human and animal studies indicating that sex and hormones affect neurotransmission in brain regions thought to be important in drug abuse (Becker 1999; Becker et al. 2001). The neurotransmitter dopamine has received the most attention, and areas of the brain that have been the focus of a majority of the investigations include the striatum and mesolimbic system.

Human studies

Little is known about the neurochemical effects of drugs of abuse in women and men. There is some evidence to suggest sex differences in the striatal dopaminergic system. For example, Mozley et al. (2001) recently reported that women have higher levels of dopamine transporters in the striatum compared to men suggesting a sex difference in dopaminergic tone. Similar results have been reported using positron emission tomography. Specifically, Pohjalainen et al. (1998) reported that women have lower striatal dopamine D_2 receptor affinity than men which may result in elevated levels of striatal dopamine in women. Sex differences in the dopaminergic system have been observed among cigarette smokers. Staley et al. (2001) examined measures of striatal dopamine transporter availability through the use of single photon emission computed tomography and found that women had higher transporter availability compared to men. However, a similar sex difference was observed among nonsmokers suggesting that this is a general finding.

While estrogen is believed to modulate dopaminergic transmission (Lindamer et al. 1997; Mozley et al. 2001), few studies have actually investigated this possibility in humans. Results from one PET study conducted by Kaufman et al. (2001) reveal that striatal dopamine D_2 receptor density does not vary across the menstrual cycle, suggesting that dopaminergic transmission may not be affected by fluctuations in ovarian hormones. Future studies are necessary to determine the effect of estrogen on dopaminergic transmission and the interaction of ovarian hormones, dopamine, and drugs of abuse.

Animal studies

There is considerable preclinical evidence that sex and ovarian hormones modulate the mesolimbic and striatal dopaminergic system. Male and female rats have different densities of dopamine D_1 and D_2 receptors in the striatum and nucleus accumbens (Andersen and Teicher 2000) and dopamine transporters in the striatum (Di Paolo et al. 1985). Walker et al. (2000) recently provided evidence of a functional sex difference in dopaminergic transmission. Specifically, they found that dopamine release and uptake is greater in female compared to male rat striatum. The effect of sex on drug-stimulated release of neurotransmitters in the striatum and nucleus accumbens has also been investigated, and the results from these studies reveal that amphetamine-induced release is greater in female than in male rats (Becker and Ramirez 1981; Castner et al. 1993; Becker 1999). Similar results have been reported for alcohol-stimulated release in the nucleus accumbens (Blanchard and Glick 1995).

Dopaminergic transmission varies with estrous cycle phase. For example, Becker and Chau (1989) reported that amphetamine-stimulated dopamine release is greatest during the estrus phase of the cycle, a time when the behavioral response is also greatest. Results obtained from OVX female rats suggest that estrogen plays an important role in modulating sex differences in neurochemical responses to psychomotor stimulants. For example, Thompson and Moss (1994) investigated estrogen's ability to modulate mesolimbic dopamine release using in vivo voltammetry, and found that OVX female rats primed with estrogen exhibited an increase in dopamine reuptake and clearance times compared to OVX vehicle treated rats. Additionally, direct infusions of estrogen into the nucleus accumbens resulted in increased dopamine levels that were significantly higher than those observed following vehicle. Estrogen may also underlie behavioral sensitization following repeated injections of psychostimulants. For example, Peris et al. (1991) exposed OVX female rats (treated with estrogen, proges-

terone, 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 revealed that OVX female rats treated with estrogen had the greatest amount of amphetamine-induced striatal [^{3}H]dopamine release compared to OVX females treated with only progesterone, or progesterone plus estrogen. These data support the hypothesis that dopamine release may be an estrogen-modulated, neurochemical substrate of repeated psychostimulant exposure.

The exact mechanism(s) by which ovarian hormones exert their effects on neurotransmitter systems that are important in drug reinforcement remains to be determined. Evidence showing that acute injections of estrogen rapidly induce locomotor activity and dopamine release suggests that these effects are not mediated by the classical estrogen receptors which usually take hours or days to produce behavioral changes (Becker et al. 2001). Becker (1999) proposed that estrogen enhances the neurochemical responses to psychostimulants in female rats through the induction of rapid changes in neuronal excitability. It was suggested that this excitability occurs when estrogen acts on intrinsic striatal GABAergic neurons to decrease the firing of recurrent collaterals synapsing on $GABA_B$ receptors on dopamine terminals. This ultimately decreases $GABA_B$ receptor stimulation which in turn enhances the release of dopamine. Estrogen has also been reported to enhance dopamine release via the downregulation of D_2 autoreceptors (for review, see Becker 1999). Studies exploring the effects of progesterone on mechanisms of action in the dopaminergic system are limited. Becker (1999) reported that progesterone enhanced dopamine release in striatal tissue from estrogen-primed OVX female rats. However, this effect of progesterone is not seen without estrogen priming and it has been suggested that progesterone may actually induce inhibitory effects on the dopaminergic system. Future research is necessary to determine how the changes induced by estrogen may act together to result in the alteration of dopaminergic neurotransmission, and if other neurotransmitter systems are involved.

Effect of ovarian hormones on pharmacokinetics

Human studies

Ovarian hormones have been reported to 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 estrogen levels are moderate and progesterone levels are high, compared to the follicular phase when estrogen levels are low to moderate and relatively unopposed by progesterone (Harris 1995). Wald et al. (1981) 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 women 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 influence the distribution of drugs of abuse in most females. Mendelson and colleagues (1999) reported that aspects of cocaine pharmacokinetics were not influenced by ovarian hormones in women. Specifically, cocaine 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.

Lammers et al. (1995) reviewed the literature on the effect of menstrual cycle phase on the pharmacokinetics of alcohol. Although several studies been conducted in this area, only two of these studies (out of 11) were designed appropriately to address this issue. Evidence from these two studies revealed that the elimination time of alcohol was increased during the luteal phase compared to other phases of the menstrual cycle. However, the effect of menstrual cycle phase was modest, producing only a 14% increase in alcohol elimination.

Animal studies

Recent research with monkeys has revealed that the pharmacokinetics of alcohol is not affected by menstrual cycle phase. Specifically, Green et al. (1999) examined the influence of sex and phase of the menstrual cycle on ethanol metabolism in cynomolgus monkeys. Male and female monkeys with a history of ethanol exposure were administered ethanol (1.0 g/kg) intragastrically on three separate occasions. Multiple blood samples were collected over a 5-h period, and sex and hormonal effects were examined. The data revealed that there was no effect of menstrual cycle on blood ethanol concentrations (BECs) or mean rates of ethanol elimination. However, consistent with findings in humans, female monkeys had faster average rates of ethanol elimination compared to males (Green et al. 1999).

One study examined the influence of ovarian hormones on the distribution to, and elimination of alcohol from the brain of female rats (Crippens et al. 1999). The authors obtained brain and vascular ethanol concentrations through microdialysis, and blood collection via the tail bleed method, respectively. The results revealed no effects of ovarian hormones on the pharmacokinetic parameters of brain ethanol concentration profiles in female rats. However, maximum blood ethanol concentrations varied across the female rats' estrous cycles. It was suggested that although circulating ovarian hormones do not influence alcohol distribution to the brain, they do influence distribution to more peripheral tissues such as the tail.

This section discussed how ovarian hormones can modulate the subjective effects/behavioral response,

intake, neurotransmission, and pharmacokinetics of some drugs. However, as Mello and Mendelson's work has shown, drugs can also affect ovarian hormones. For example, both cocaine and alcohol have been shown to cause disruptions of the menstrual cycle in both women and nonhuman primates and of the estrous cycle in rodents (for reviews, see Mello et al. 1989; Mello and Mendelson 1997). Drugs acting via the opioid system have also been reported to produce menstrual dysfunction in women. For example, Santen et al. (1975) obtained menstrual cycle histories from 76 former heroin addicts that were receiving daily methadone maintenance and found that more that 50% of these women had experienced menstrual cycle abnormalities while on opiates.

Treatment

Human studies

The majority of investigations regarding treatment for drug abuse have focused on males. Typically, drug abuse rehabilitation centers and facilities have been concerned with the needs of males. The lack of sex specific treatment facilities and research studies on success rates provides little information on how to target sex specific issues that drug abusers may encounter (Brady and Randall 1999).

Some sex differences have been reported in the treatment outcomes and resources for drug abuse and dependence disorders. Specifically, it has been reported that women are more likely to seek treatment for their drug abuse problems in mental health facilities versus facilities specifically designed to treat drug abuse. This may be due to the high rates of comorbidity in women between drug abuse and psychiatric disorders (e.g. affective, anxiety, and psychosexual disorders). Women also tend to enter drug abuse treatment for different reasons than men. Usually women decide to seek treatment due to child-rearing issues, while men are more likely to seek treatment after job-related consequences from their drug abuse. Lack of funding, childcare resources and transportation are barriers that women encounter when contemplating seeking treatment for drug abuse. Similarly, the negative stigma associated with drug abuse and child custody issues inhibits women drug abusers from seeking treatment (for reviews see Greenfield 1996; Brady and Randall 1999).

Women possess an array of risk factors that are associated with relapse to drug use after treatment, including depression, anxiety, and low self-esteem (Fiorentine et al. 1997). Despite these risk factors, results from clinical studies indicate that following treatment women do just as well as men at remaining abstinent, if not better (Anglin et al. 1987; Hser et al. 1990; Kosten et al. 1993; Gil-Rivas et al. 1996; Pettinati et al. 1997; Weiss et al. 1997). An exception appears to be for abstinence rates among smokers. Clinical studies have consistently reported that women have lower rates of smoking cessation compared to men following behavioral or combined behavioral/nicotine replacement approaches or following unaided quit attempts (Perkins et al. 1999). Differential treatment outcome may be due to "real" biologic sex differences or to differences in sociocultural factors. Prospective treatment outcome studies that compare approximately equal numbers of men and women are needed to establish whether or not specific treatments differentially affect females and males. Furthermore, animal models of potential treatment are useful for assessing the contribution of sociocultural versus biological factors in sex-specific differences in treatment outcomes.

Animal studies

Initial animal work with potential behavioral and pharmacological treatments for drug abuse has, in fact, revealed sex differences. In an experiment with rats, baclofen, a $GABA_B$ agonist, was administered during the acquisition of IV cocaine self-administration and the rate of acquisition was compared in females and males (Campbell et al. 2002). Earlier work had shown that the effects of baclofen and other potential treatment drugs are more effective during transition states such as acquisition or reinstatement, and higher treatment drug doses are needed to suppress maintenance levels of drug self-administration (Campbell et al. 1999). Therefore, the effects of baclofen on IV cocaine self-administration in female and male rats were compared during this phase. Rats were trained to self-administer a relatively low dose (0.2 mg/kg) of IV cocaine under a fixed-ratio 1 (FR1) schedule using an autoshaping procedure. The criterion for acquisition was a mean of 100 self-administered infusions over 5 consecutive days. Groups of females and males were pretreated with IP injections of baclofen (2.5 mg/kg) or vehicle 30 min prior to each daily session. Baclofen decreased the rate of acquisition of cocaine self-administration and the percentage of animals in the group meeting the acquisition criterion in both female and male groups. However the effects were more pronounced in females. A smaller percentage of baclofen-treated females (15.4%) than males (77.7%) met the acquisition criterion compared to 100% in vehicle-pretreated males and females.

Similar results were obtained in another study using a different treatment drug, ketoconazole in the early maintenance phase of IV heroin self-administration (Carroll et al. 2001). Ketoconazole is an inhibitor of corticosterone synthesis, and it was used to determine whether increases in heroin self-administration due to food restriction were related to a stress response. Rats were trained to self-administer IV heroin (0.015 mg/kg) with a similar autoshaping procedure. After the criterion for acquisition was met (a mean of 20 infusions over 5 days), self-administration continued under an FR1 schedule during daily 23-h sessions. Every third day the animals were food restricted for a total of four 11-day

cycles. Both females and males nearly doubled their heroin infusions when they were food-restricted, compared to the two intervening days of food satiation. Ketoconazole significantly suppressed this elevation of drug intake in females but not in males. When exogenous corticosterone was administered to females in addition to ketoconazole, the food-restricted increases in heroin self-administration were reinstated. These data show a greater treatment effect in females than in males, and the data concur with previous reports that there is an interaction between feeding, stress and sex in rats with respect to the effects of drugs of abuse (Klein et al. 1997).

A third medication study was recently conducted in rhesus monkeys orally self-administering PCP and pretreated with bremazocine, a kappa opioid agonist (unpublished data). Bremazocine dose-dependently reduced PCP self-administration in both females and males, but the percent reductions from baseline were greater in females (25.6, 46.6, 83.9%) than males (0.6, 26.9, 83.9%) at two of the three bremazocine treatment doses tested (0.32, 1.0, and 2.5 g/kg), respectively.

In addition to differential effects of pharmacological treatments as a function of sex, there is initial evidence that female and male rats respond differently to behavioral interventions for drug self-administration. Initial reports using male rats indicate that access to a running wheel reduces oral alcohol (McMillan et al. 1995) and amphetamine (Kanarek et al. 1995) intake. The effects of access to wheel-running were extended to IV cocaine self-administration and compared in female and male rats (Cosgrove et al., unpublished data). Rats had been trained to self-administer a low dose of cocaine (0.2 mg/kg) during daily 6-h sessions using an autoshaping procedure and a criterion of 100 infusions a day for 5 days. Baseline levels of cocaine infusions were slightly higher in females than males. When the groups were allowed access to a running-wheel, cocaine-infusions were reduced in both females and males; however, the reductions were proportionally much greater in females. Similar findings have recently been reported observed relating to the suppressant effect of saccharin on oral PCP self-administration in rhesus monkeys (Casgrove and Carroll, unpublished data). These results are consistent with findings that female rats show a greater effect of pharmacological treatment than males, and they suggest that nondrug alternative reinforcers may be especially effective in the treatment of female drug abusers.

Conclusion

There are many reports of sex differences in drug abuse in animals and humans. It is apparent that sex influences the behaviors induced by drugs, as well as the pharmacological responses to drugs. Future research examining the factors that underlie sex differences may allow for the development of safe and effective sex-specific behavioral and pharmacological therapies for drug abuse. It is important to consider ovarian hormonal influences on responses to drugs of abuse when developing pharmacotherapies for drug abuse treatment in women. There is a need for future research in this area, as well as on how men and women differ in their responses to different treatment programs and methods. New studies on treatment effectiveness are needed in order to assess sex differences in response to different treatment strategies. The research makes clear that there are sex differences in drug abuse and although studies in this field have begun to focus on male and female differences in drug abuse, more research is necessary in order to elucidate the mechanisms underlying these observed sex differences.

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