Review TRENDS in Pharmacological Sciences Vol.25 No.5 May 2004

Sex and estrogen influence drug abuse

Marilyn E. Carroll[1], Wendy J. Lynch[2], Megan E. Roth[1], Andrew D. Morgan[1] and Kelly P. Cosgrove[2]

[1]Department of Psychiatry, Mayo Box 392, University of Minnesota, Minneapolis, MN 55455, USA
[2]Yale University School of Medicine, Department of Psychiatry, 34 Park Street, New Haven, CT 06508, USA

Evidence is accumulating that the etiology, epidemiology, consequences and mechanisms that underlie drug abuse are different in males and females. In this review, we present examples of sex differences in all phases of drug abuse, including acquisition, steady-state maintenance, escalation, dysregulation, withdrawal, relapse and treatment. Most reported findings are based on laboratory research in animals, but there are corroborating reports from human clinical and epidemiological studies. In all phases of drug abuse, females seem to be more sensitive to the rewarding effects of drugs than males, and estrogen is a major factor that underlies these sex differences.

Recent reports from animal and clinical research indicate that females are more susceptible to problems of drug abuse than males [1]. These findings contrast with the general observation that more adult men than women are involved in illicit drug [2] and alcohol abuse [3]. However, the gender gap narrows in adolescents to reveal equal rates of alcohol and illicit drug use in males and females, and the greater use of cigarettes and non-medical prescription drugs in females [2]. The more rapid increase in the use of all drugs of abuse (except alcohol) by women compared with men might reflect changing sociocultural patterns [1], but it is consistent with findings from experiments in laboratory animals, which indicate that there are true differences between the biological sexes. The term sex defines males and females based on reproductive organs and chromosomes. Gender, which is used more often in humans, refers to how one views ones identity.

There are also differences in the patterns of drug abuse between men and women. Women progress from opportunity to use and drug abuse faster than men [3,4], which is similar to the accelerated progression of gambling [5]. Women might also be more vulnerable to the adverse health effects of drugs than men [6,7], and they are more likely than men to seek treatment for alcohol and drug abuse [3]. Once in treatment for drug abuse, women are either as good as or better than men at remaining abstinent (except for tobacco smoking) [1]. Analysis of sex differences in drug abuse might be biased by retrospective self reports, cultural influences and psychiatric comorbidities. Thus, animal models are most useful for studying sex differences and their underlying mechanisms at different phases of drug abuse. Although animal models are free of psychiatric comorbidities, it is possible to select animals on measures of emotionality, hyperactivity, impulsivity and other factors that serve as models for human psychiatric disorders. However, sex differences in these comorbidities have not yet been examined.

Rewarding effects of drugs

There are sex differences in animal models of all phases of drug abuse, including acquisition, maintenance, escalation, dependence, withdrawal, reinstatement (relapse) and treatment. Figure 1 presents a schematic of the phases of drug abuse that have been modeled and studied with respect to sex and hormonal effects. Most commonly, a traditional, operant-conditioning animal model is used to study drug abuse in laboratory studies of animals and humans. Animals are implanted with an intravenous (i.v.) catheter and trained to give operant responses that produce drug deliveries.

Acquisition

The acquisition of drug abuse is the transition from initial sampling to continued regular use (reviewed in [8]). In

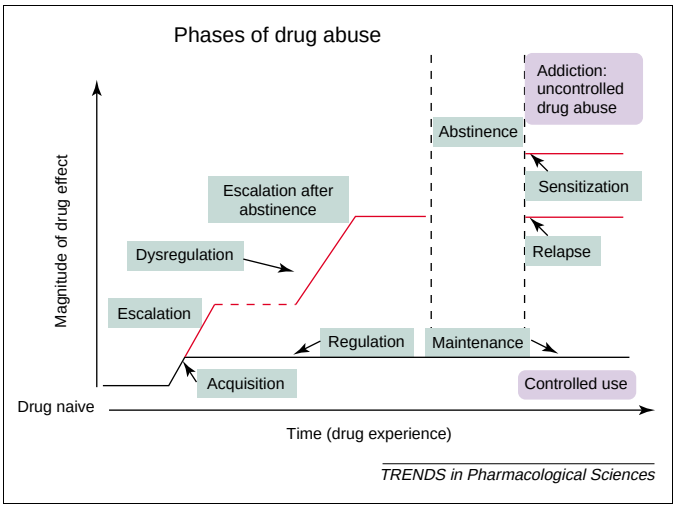

Figure 1. The major phases in the development of drug abuse modeled in laboratory animals. After initial exposure and acquisition of drug taking in drug-naïve animals, intake can stabilize at low levels. This leads to long-term, controlled use. However, more often, drug intake escalates over time and, although there might be periods of either controlled use or abstinence, escalation driven by craving and binge use can return. After a period of forced abstinence, relapse can occur, usually at the levels of abuse that were present before abstinence. Alternatively, animals might experience sensitization and experience an enhanced effect from the same amount of drug that was used before abstinence. This is thought to be a marker of dependence. It is important to study factors that are related to drug abuse as well as potential treatments at each of these phases, because behavioral and pharmacological prevention and intervention strategies could have different, possibly opposite, effects during different phases.

Corresponding author: Marilyn E. Carroll (mcarroll@umn.edu).

 0165-6147/$ - see front matter doi:10.1016/j.tips.2004.03.011

animals, acquisition of drug self-administration is evaluated by several techniques such as autoshaping (automatic priming infusions), experimenter-administered priming injections and simple exposure [8]. Reviews of the literature [1,8] indicate that female rats acquire i.v. self-administration of cocaine [9], methamphetamine [10] and nicotine [11] faster than males. Although a higher percentage of females meet acquisition criteria for cocaine and methamphetamine self-administration (Table 1), male and female rats acquire heroin self-administration at equal rates. There are mixed reports of sex differences in the acquisition of i.v. self-administration of heroin in rats [8]. Higher oral intake of caffeine also occurs in female rats when food intake is limited [1].

There are mixed findings on the acquisition of ethanol self-administration in non-human primates. As reviewed in [1], sex differences are not observed in juvenile rhesus monkeys, and in drug-experienced and drug-naïve rhesus monkeys. However, female vervet monkeys self-administer more ethanol than males. This difference could be caused by either species or procedural differences (e.g. dose). In another study, more female rhesus monkeys (100%) acquired phencyclidine (PCP) self-administration than males (36.4%) using a low drug concentration.

In studies of sexually mature, drug-naïve rats and monkeys, sex differences in acquisition occur more reliably with low doses of some classes of drugs (e.g. stimulants and NMDA receptor antagonists) than others (e.g. ethanol and opioids). Other important factors are the response requirement and availability of environmental cues. For example, enhancement of nicotine-maintained responding was reported in females at a low dose (0.03 mg kg^{-1}) at a fixed-ratio 5 (FR5) schedule (five responses per drug delivery) versus FR1 schedule, and visual stimuli enhanced the sex differences [11].

Maintenance

Maintenance is a period of steady-state, well-regulated, drug self-administration after the initial acceleration of drug-maintained responding during acquisition (Figure 1) [1]. When male and female rats are compared during a maintenance phase on a simple FR1 schedule, there are no sex differences in cocaine, heroin and methamphetamine self-administration. However, more females than males acquire cocaine self-administration (Table 1), and females exceed males in their drug self-administration during maintenance under progressive-ratio (PR) schedules (in which each successive drug delivery is contingent on a greater number of responses).

Table 1. Sex differences in the acquisition and maintenance of drug self-administration

	Cocaine (0.2 mg kg^{-1})	Methamphetamine (0.02 mg kg^{-1})	Heroin (0.015 mg kg^{-1})
Acquisition: percentage of group meeting acquisition criterion			
Males	30.0	11.1	91.7
Females	70.0[a]	55.0[a]	90.0
Acquisition: number of days to meet acquisition criterion[b]			
Males	16.7 ± 0.7	29.0 ± 1.5	13.0 ± 2.1
Females	7.6 ± 1.6[a]	18.0 ± 0.5[a]	8.7 ± 2.4
Maintenance: number of infusions in days 25–30[b]			
Males	150 ± 20	170 ± 0	35 ± 5
Females	185 ± 22	160 ± 25	40 ± 6

[a]Significant sex differences ($P < 0.05$).
[b]Mean ± SEM.

Escalation and dysregulation

In animals, several methods have been used to model the escalation from controlled to uncontrolled drug use, such as increasing the dose, session length and number of trials [12]. Sex differences are reported using a two-lever procedure that allows rats to increase their dose of cocaine by responding (FR1) on one lever and to decrease dose by responding (FR1) on the other lever [12]. Regulation, defined as a correlation between the size of the self-administered dose and the time until the response for the next infusion, was shorter and less precisely regulated based on the previous dose in females than in males. This resulted in latencies between doses, more frequent selection of higher doses and overall higher intake (mg kg^{-1}) in females [12].

A different method allows 24-h access to drug in discrete 10-min trials. Under this procedure 'binge' and dysregulated patterns of intake have been reported in male rats when drug access is relatively frequent (four trials h^{-1}) [13] and, in a later study, female rats self-administered more cocaine with longer initial 'binge' length and greater loss of circadian control over intake (mg kg^{-1}) than males [14]. Cocaine-maintained behavior was higher in female than male rats during a subsequent PR schedule [14].

Another model of escalation extends the duration of drug access (e.g. from 1 h to 6 h per day) [15]. During periods of short access, cocaine infusions are relatively stable in female and male rats, but with longer sessions, females increase their intake at a higher rate than males (M.E. Roth and M.E. Carroll, unpublished). In later studies in which rats from both groups were given 3-h access to cocaine, infusions were higher in females than males in the groups that had previously had access to cocaine (0.5 mg kg^{-1}) for 6 h. After escalation, cocaine intake increased under a FR1 in both male and female rats, but there was no difference between the sexes. Thus, animal data indicate that females exceed males in escalation, dysregulation and binge-like patterns of cocaine self-administration, which is more likely to be revealed under a challenging behavioral schedule (e.g. PR) rather than an FR1. Studies in humans indicate that women progress to uncontrolled drug use faster than men [4].

Dependence and withdrawal

Although there are few studies in this area, initial findings indicate that female rats are either slower or less likely to develop dependence on ethanol [16] and morphine [17] than males, and they are quicker to recover [16].

Reinstatement and relapse

In rats, a reinstatement procedure [18] to model relapse has revealed sex differences in drug-seeking behavior [19]. In this procedure, animals were trained to self-administer a drug such as cocaine that was later replaced by saline. Later, a single priming injection, exposure to physical stress or presentation of environmental cues reinstated

drug-seeking behavior [18]. Female rats showed more extinction responding on the drug-associated lever after drug removal and greater reinstatement after a priming injection than males, and responding was reinstated at a lower priming dose than in males [18]. In humans, cocaine-related cues induce more craving in female than in male addicts [20]. Women are more affected by internal cues for smoking maintenance and relapse, such as stress and depression, and men by external, environmental cues [7]. Similar sex differences apply to alcohol and cocaine abuse [1].

Sex differences in behaviors related to drug abuse

One possibility that could account for the differences in drug abuse between the sexes is that females might show a higher general activity level, greater sensitivity to drugs and enhanced reward incentive. In fact, sex differences exist in behavior maintained by non-drug rewards (reinforcement).

Conditioned place preference (CPP)

Another animal model for assessing the rewarding effects of drugs is based on the assumption that the environment in which a drug is administered becomes associated with its positive attributes. CPP occurs when a rat returns to and spends more time in a place where it had been previously administered drug rather than a place where it had received the vehicle injection [1]. Female rats acquire a cocaine-induced CPP in fewer sessions and at lower doses than males [21]. Similar findings are reported for morphine [22].

Intracranial self-stimulation (ICSS)

Electrical self-stimulation of several brain areas is rewarding to rats and non-human primates, and it activates brain areas that are implicated in drug abuse. Female rats showed higher rates of ICSS than males in the lateral hypothalamus, but other studies have shown no sex differences [23].

Dietary preferences

Dietary preference in rats, particularly avidity for sweets and fats, predicts vulnerability to drug abuse [24], and female rats consume more sweetened liquids than males [25]. There is also evidence of a relationship between preferences for sweets and other carbohydrates in humans and relapse in abstinent, drug abusers [26].

Locomotor activity

In rats, locomotor activity correlates positively with vulnerability to self-administration of psychostimulants [1]. Females move and explore more than males, which indicates a link between locomotion, sex and drug abuse [1,24]. However, other data indicate no differences between the sexes in either locomotor activity or operant lever-pressing [1]. Another activity that predicts drug abuse and is rewarding in itself is wheel-running, and female rats outrun males.

Sensitization

Female rats also have an increased, more rapid and longer lasting locomotor response to psychostimulants compared to males [27–29]. Repeated administration of psychostimulants produces an elevated response then, after a week or more of no drug, a further increase (known as sensitization) when an animal is challenged with a stimulant (Figure 1). This effect is stronger in female than male rodents [30]. Stimulant sensitization is thought to be involved in the development of drug dependence and is associated with relapse [31] and is thought to be regulated by central transmission of dopamine and other neurotransmitters that are implicated in stimulant reinforcement. These processes might differ between male and female rodents [32]. Data on sex differences of the sensitizing effects of other drugs of abuse (e.g. opioids) are equivocal [1].

Overall, there are many similarities in the sex differences observed with drugs of abuse and other hedonic states, such as the ingestion of sweets, place preference, ICSS and locomotor activity. This indicates that common reward mechanisms underlie these events, and that biological mechanisms of reward might differ in males and females.

The biological bases of sex differences in drug abuse

Several mechanisms, either alone or in combination, might be responsible for differences in drug abuse. First, there may be peripheral sex differences (e.g. percent body fat and metabolic rate) that are related to the pharmacokinetics of abused drugs. Second, there might be differences in the structural and functional organization of the brain (e.g. reward neurocircuitry) that transcends reproductive functions. Third, circulating sex hormones might either facilitate or impede the drug-abuse process.

Pharmacokinetics

Evidence for sex differences in the pharmacokinetic and pharmacodynamic actions of drugs is mixed. There are no differences in the concentrations of cocaine in the brain after equivalent doses in male and female rats [33] but female cynomologous monkeys eliminate ethanol faster than males. When equivalent i.v. doses of cocaine are administered to rats, males exhibit toxic reactions that are more severe than those in females [34]. In one study in humans no sex differences in the peak plasma levels, elimination half-life and cardiovascular effects of cocaine were shown [35]. However, Lukas *et al.* [36] reported higher peak-plasma levels of cocaine, faster detection, and more episodes of the good and bad effects of cocaine in males than females. During the follicular phase of the menstrual cycle (high estrogen), women have higher peak-plasma levels of cocaine than during the luteal phase (elevated estrogen and progesterone) [36]. In an earlier study, benzodiazepines have a longer half-life in females than males [37].

Neurotransmission

There are sex-related differences in neurotransmission that underlie the behavioral effects of drugs of abuse [32]. For example, the rates of release and uptake of dopamine in the caudate nucleus are greater in females than males and the density of striatal dopamine receptors is higher [1]. Castrated male rats have lower concentrations of

dopamine relative to ovariectomized (OVX) female rats in other areas of the brain (e.g. medulla, pons and hypothalamus) [1,38], which indicates that differences in the development of the brain in males and females might account for differences in drug abuse [32,39]. Studies of behavior and c-Fos induction also indicate sex differences in the responses to morphine (male > female) and NMDA receptor antagonists (female > male) [40].

Data from rat studies indicate that ovarian hormones regulate the neuronal activity that is associated with drugs of abuse; thus, circulating hormones might be as important as developmental sexual dimorphism in explaining differences in drug abuse. Although these hormones include testosterone in males, and estrogen and progesterone in females, the existing research focuses mainly on estrogen [1,39]. Imaging studies in humans support the importance of the midbrain dopamine-containing neurons in drug abuse. Studies of dopamine binding show greater dopamine displacement in key brain areas in women than men [41] and greater availability of dopamine transporters [42].

Effects of estrogen

In animal studies, estrogen enhances drug-seeking behavior in all phases of drug abuse that show sex differences, but there is little evidence for a role of other sex hormones, such as progesterone in females and testosterone in males. Two main paradigms are used to study hormonal influences in animals: (i) the phase of either the estrous (rodents) or menstrual (primates) cycle; and (ii) hormone levels are manipulated by ovariectomy in females and castration in males, and animals receive controlled, hormone-replacement. Intact animals can also be treated with either estrogen or estrogen receptor antagonists such as tamoxifen.

Acquisition

In one study of i.v. self-administration of cocaine, female rats were either OVX or sham operated and treated with either estrogen or vehicle. In addition, groups of intact females were either treated with tamoxifen or vehicle [1]. Both sham and OVX plus estrogen groups acquired i.v. self-administration of cocaine more rapidly, and a higher percentage of the groups met the criterion (100 infusions per day) compared with OVX and tamoxifen-treated groups. In a similar study, OVX rats treated with estrogen acquired heroin self-administration faster than OVX rats [1]. Recent work confirms that estradiol facilitates cocaine acquisition and that acquisition is enhanced in gonadectomized females compared with males. These data indicate innate differences in brain organization [43].

Maintenance

As seen in Table 1, sex differences in self-administration of drug during the maintenance phase is not as large as during the acquisition phase. Differences as a result of estrogen (OVX versus OVX plus estrogen) were also less apparent during maintenance than during acquisition, particularly under a simple FR1 schedule in rats [1]. However, with a PR schedule, self-administration of cocaine (but not heroin) was elevated during the estrus phase (when peak estrogen levels decline) [1]. When a two-lever, dose-regulation paradigm was used, female rats showed the greatest dysregulation of cocaine-self-administration during estrus and they consumed nearly twice the amount as during other phases [44].

Non-drug rewards

There is a large literature that shows several effects of ovarian hormones such as estrogen on taste preferences in animals [45] and humans [46]. A study of the effect of estrogen during different phases of the estrous cycle reveals that ICSS rates in the hypothalamus increase when estrogen is high (proestrus–estrus) and during estrogen replacement in OVX rats [1]. Similar results have been reported for ICSS of other brain areas. Wheel-running activity, anxiety and fear learning also increased after estrogen treatment in OVX rats compared to vehicle-treated controls [47].

Locomotor activity

There are few studies of hormonal influences on activity level [1]. Wheel running in rats increases during estrus relative to other phases. Cocaine-stimulated locomotor activity is highest during the high estrogen, proestrus and estrus, phases and when estrogen was administered to intact rats [28,30]. OVX rats did not show cocaine sensitization, but OVX rats supplemented with either estrogen or estrogen plus progesterone displayed enhanced locomotor activity compared to progesterone alone and no replacement groups [48].

Sensitization

Cocaine-induced sensitization of locomotor activity increases in estrogen-treated OVX rats compared with vehicle controls and those treated with either estrogen plus progesterone or progesterone alone. Furthermore, cocaine-induced sensitization in OVX rats treated with estrogen and progesterone is enhanced compared with males [48]. Consistent with these findings, there are no sex differences in cocaine-induced behavioral sensitization in young, sexually immature rats [49]. Others have shown that sex differences and hormonal effects vary with the behavioral measure (e.g. locomotion and stereotypy) [29]. Sensitization also persists in OVX rats without estrogen [30].

Ovarian hormones and pharmacokinetics

Estrogen might exert its effects by altering pharmacokinetics. Studies of ethanol intake in monkeys reveal no effect of the menstrual cycle on ethanol concentration in the blood [50] and, in rats ovarian hormones had no effect on the pharmacokinetic parameters of ethanol [51]. Some studies in humans indicate that changes in the menstrual cycle are related to differential bioavailability of drugs [1], but others report no differences in the pharmacokinetics of cocaine in women during the follicular (high estrogen) and mid-luteal (high estrogen and progesterone) phases [35].

Ovarian hormones and neurotransmission

Ovarian hormones influence cocaine reward by altering

monoamine neurotransmitter systems in the striatum and mesolimbic brain areas [32,52], which are considered to include the main reward circuitry [53]. For example, progesterone enhances the release of dopamine in striatal tissue in estrogen-primed rats but not in unprimed controls [32]. Similar results are observed in rats following repeated cocaine exposure and amphetamine-stimulated dopamine release from the striatum [1,32]. Estrogen or progesterone produced the greatest release of dopamine. Others have reported that uptake of dopamine in the striatum varies with the estrous cycle in rat and that it increases during the morning of proestrus (estrogen rising) [54]. Dopamine and 5-hydroxytryptamine concentrations decrease in the ventral tegmental area in OVX females. Progesterone replacement increases the concentration of dopamine in this area and estrogen decreased dopamine levels in the nucleus accumbens [52].

Drug-abuse treatment

Experimental and clinical research on the treatment of drug abuse has focused mainly on males. Studies in laboratory animals and prospective, treatment outcome and treatment/hormonal interaction studies in humans are needed to fully evaluate sex differences in the treatment of drug abuse. Animal models have been developed to evaluate the effectiveness of treatment for drug abuse and the results often predict success in human treatment.

Behavioral

One behavioral treatment studied in rats is to use an alternative, non-drug rewarding activity (wheel-running) to reduce ongoing i.v. cocaine self-administration [55]. Access to the wheel in the operant chamber reduces cocaine infusions in both males and females, with a significantly greater effect in females (Figure 2). In monkeys, the use of saccharin as a concurrent non-drug alternative for orally delivered PCP, reduced drug intake more in females than males (Figure 2) [56].

Pharmacological

In tests of pharmacological treatments in rats and monkeys, self-administration of cocaine and heroin was reduced more in female than in male rats treated with baclofen [57], a $GABA_B$ receptor agonist (Figure 2b), and ketoconazole, an inhibitor of corticosterone synthesis (Figure 2c), respectively [1]. In adult monkeys, bremazocine [58], a kappa opioid peptide (KOP) receptor agonist, attenuated oral self-administration of PCP to a greater extent in females than in males (Figure 2e). In mice, a KOP receptor agonist reduced cocaine-induced locomotor stimulation in female but not male mice [59]. Women exhibit greater analgesia than men after treatment with KOP receptor agonists. Clinical studies of treatment outcome indicate that women have more risk factors (e.g. anxiety and depression) that are related positively to relapse [1]. However, once in treatment, they do either as well as or better than men [1], except for tobacco smoking [51].

Concluding remarks

Sex differences occur in all phases of drug abuse, from the initial acquisition of drug self-administration in drug-naïve animals, to maintenance, escalation and relapse. Female animals appear to be more sensitive to the rewarding effects of drugs than males throughout these phases, and estrogen seems to be a determining factor. Females are also affected more by behaviors that are related to drug abuse such as CPP, ICSS, intake of preferred dietary substances, locomotor activity and stimulant-induced sensitization. This indicates that estrogen might have a more general role in modulating reward. Sex differences in drug abuse are more likely to be evident when the drug dose is low, during transition phases of addiction, under a challenging behavioral schedule and in sexually mature animals. Generally, prospective animal studies agree with initial epidemiological reports in humans, which show that females progress from drug-use opportunity to abuse faster than males, but that they respond either as well as or better than males to

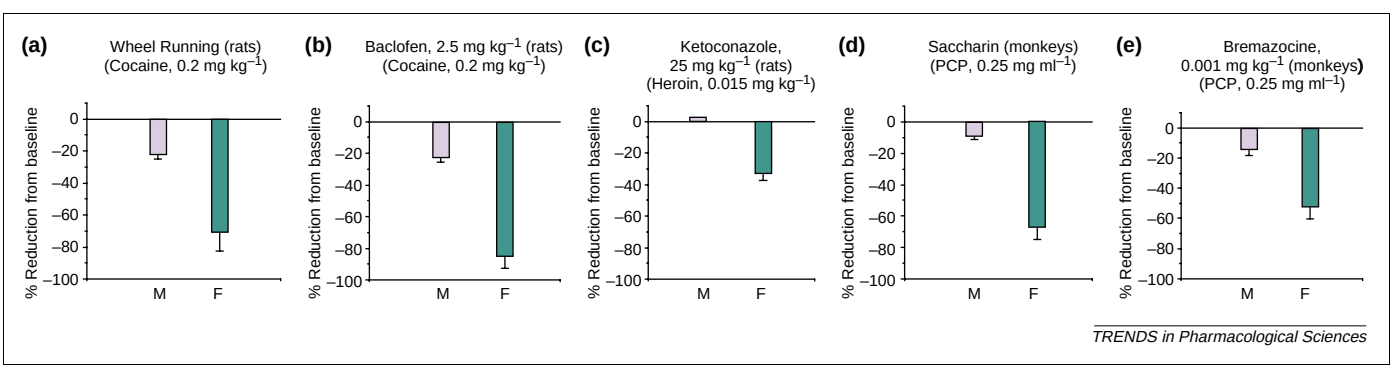

Figure 2. Reduction in self-administration of drugs during treatment. The effects of treatment in males and females are shown in five experiments conducted in rats **(a–c)** and monkeys **(d,e)**. (a,d) Behavioral treatments in which a non-drug alternative reinforcer was available concurrently with access to drug self-administration for at least 10 days are shown. Results are compared with a previous period of stable behaviour when the non-drug alternative was not available. (b,c,e) The effects of pharmacological treatments in which the treatment medication was injected before the drug self-administration session for five consecutive days are shown. Data are expressed as the reduction from the baseline condition before each specific treatment. Treatment occurred during the steady-state maintenance phase (c,e) or was injected during the acquisition (autoshaping) phase until either the acquisition criterion was met or 30 days elapsed if it was not met (b). In this case, the reduction refers to the percentage of animals per group that met the acquisition criterion compared with the saline-treated controls in which 100% met the criterion. Data are calculated and redrawn from [55] (a), [57] (b), [9] (c), [56] (d) and [58] (e).

treatment. More research is needed to develop treatments that acknowledge sex and hormonal effects.

Acknowledgements

We are grateful to Maria Arrizi, Isadora Rosario-Gonzalez, Tina Gremmel, Kate Klammer, Erin Larson, Annemarie Loth, Lisa Normile and Craig Slapinski who contributed to the research into gender differences in drug abuse in our laboratory. Preparation of this manuscript was supported by National Institute on Drug Abuse grants KO5 DA15267, RO1 DA 03240 (MEC), F31 DA 11717 (WJL), F31 DA 14161 (MER), F31 DA 005575 (KPC) and T32 DA 07097 (ADM).

References

1 Lynch, W.J. *et al.* (2002) Biological basis of sex differences in drug abuse: preclinical and clinical studies. *Psychopharmacology (Berl.)* 164, 121–137
2 Substance Abuse and Mental Health Services Administration (SAMHSA) (2001) Summary of Findings from the 2000 National Household Survey on Drug Abuse. Office of Applied Studies, NHSDA Series H-13, DHHS Publication No. (SMA) 01-3549. Rockville, MD, USA
3 Brady, K.T. and Randall, C.L. (1999) Gender differences in substance use disorders. *Psychiatr. Clin. North Am.* 22, 241–252
4 Randall, C. *et al.* (1999) Telescoping of landmark events associated with drinking: a gender comparison. *J. Stud. Alcohol* 60, 252–260
5 Potenza, M.N. *et al.* (2001) Gender-related differences in the characteristics of problem gamblers using a gambling helpline. *Am. J. Psychiatry* 158, 1500–1505
6 Jarque-Lopez, A. *et al.* (2001) Prevalence and mortality of heavy drinkers in a general medical hospital unit. *Alcohol Alcohol.* 36, 335–338
7 Perkins, K.A. *et al.* (2001) Sex differences in the subjective and reinforcing effects of visual and olfactory cigarette smoke stimuli. *Nicotine Tob. Res.* 3, 141–150
8 Campbell, U.C. and Carroll, M.E. (2000) Acquisition of drug self-administration: environmental and pharmacological interventions. *Exp. Clin. Psychopharmacol.* 8, 312–325
9 Carroll, M.E. *et al.* (2001) Ketoconazole suppresses food restriction-induced increases in heroin self-administration in rats: sex differences. *Exp. Clin. Psychopharmacol.* 9, 307–316
10 Roth, M.E. and Carroll, M.E. Acquisition and maintenance of intravenous methamphetamine self-administration in rats: effects of sex and the estrous cycle. (in press)
11 Caggiula, A.R. *et al.* (2002) Environmental stimuli promote the acquisition of nicotine self-administration in rats. *Psychopharmacology (Berl.)* 163, 230–237
12 Lynch, W.J. *et al.* (1998) A novel paradigm to investigate regulation of drug intake in rats self-administering cocaine or heroin intravenously. *Exp. Clin. Psychopharmacol.* 6, 22–31
13 Morgan, D. *et al.* (2002) Increases in the reinforcing efficacy of cocaine after particular histories of reinforcement. *Behav. Pharmacol.* 13, 389–396
14 Lynch, W.J. and Taylor, T. Sex differences in the behavioral effects of 24-h access to cocaine under a discrete trial procedure. *Neuropsychopharmacology* (in press)
15 Ahmed, S.H. and Koob, G.F. (1999) Long-lasting increase in the set point for cocaine self-administration after escalation in rats. *Psychopharmacology (Berl.)* 146, 303–312
16 Devaud, L.L. and Chadda, R. (2001) Sex differences in rats in the development of an recovery from ethanol dependence assessed by changes in seizure susceptibility. *Alcohol. Clin. Exp. Res.* 25, 1689–1696
17 Cicero, T.J. *et al.* (2002) Gender-linked differences in the expression of physical dependence in the rat. *Pharmacol. Biochem. Behav.* 72, 691–697
18 Carroll, M.E. and Comer, S.D. (1996) Animal models of relapse. *Exp. Clin. Psychopharmacol.* 4, 11
19 Lynch, W.J. and Carroll, M.E. (2000) Reinstatement of cocaine self-administration in rats: sex differences. *Psychopharmacology (Berl.)* 148, 196–200
20 Robbins, S.J. *et al.* (1999) Comparing levels of cocaine cue reactivity in male and female outpatients. *Drug Alcohol Depend.* 53, 223–230
21 Russo, S.J. *et al.* (2003) Sex differences in the conditioned rewarding effects of cocaine. *Brain Res.* 970, 214–220
22 Randall, C.K. *et al.* (1998) Morphine-induced conditioned place preference in preweanling and adult rats. *Pharmacol. Biochem. Behav.* 60, 217–222
23 Craft, R.M. *et al.* (2001) Effects of chronic morphine treatment on responding for intracranial stimulation in female versus male rats. *Exp. Clin. Psychopharmacol.* 9, 198–208
24 Tropp, J. and Markus, E.J. (2001) Sex differences in the dynamics of cue utilization and exploratory behavior. *Behav. Brain Res.* 119, 143–154
25 Klebaur, J.E. *et al.* (2001) Individual differences in behavioral responses to novelty and amphetamine self-administration in male and female rats. *Behav. Pharmacol.* 12, 267–275
26 Carroll, M.E. (1999) Interactions between food and addiction. In *Neurobehavioral Toxicology and Addiction: Food, Drugs and Environment* (Niesink, R.J.M. *et al.*, eds), pp. 286–311, CRC Press
27 Chin, J. *et al.* (2002) Endogenous gonadal hormones modulate behavioral and neurochemical responses to acute and chronic cocaine administration. *Brain Res.* 945, 123–130
28 Sell, S.L. *et al.* (2000) Influence of ovarian hormones and estrous cycle on the behavioral response to cocaine in female rats. *J. Pharmacol. Exp. Ther.* 293, 879–886
29 Walker, M.B. *et al.* (2000) Dopamine release and uptake are greater in female than male rat striatum as measured by fast cyclic voltammetry. *Neuroscience* 95, 1061–1070
30 Hu, M. and Becker, J.B. (2003) Effects of sex and estrogen on behavioral sensitization to cocaine in rats. *J. Neurosci.* 23, 693–699
31 Robinson, T.E. and Berridge, K.C. (2000) Mechanisms of action of addictive stimuli: Incentive sensitization and addiction. *Addiction* 96, 103–114
32 Becker, J.B. (1999) Gender differences in dopaminergic function in striatum and nucleus accumbens. *Pharmacol. Biochem. Behav.* 64, 803–812
33 Bowman, B.P. *et al.* (1999) Effects of sex and gonadectomy of cocaine metabolism in the rat. *J. Pharmacol. Exp. Ther.* 290, 1316–1323
34 Morishima, H.O. *et al.* (1993) Gender-related differences in cocaine toxicity in the rat. *J. Lab. Clin. Med.* 122, 157–163
35 Mendelson, J.H. *et al.* (1999) Cocaine pharmacokinetics in men and in women during the follicular and luteal phases of the menstrual cycle. *Neuropsychopharmacology* 21, 294–303
36 Lukas, S.E. *et al.* (1996) Sex differences in plasma cocaine levels and subjective effects after acute cocaine administration in human volunteers. *Psychopharmacology (Berl.)* 125, 346–354
37 Wilson, M.A. (1992) Influences of gender, gonadectomy, and estrous cycle on GABA/BZ receptors and benzodiazepine responses in rats. *Brain Res. Bull.* 29, 165–172
38 Das, A. and Chaudhuri, S.K. (1995) Effects of sex steroids on the concentrations of some brain neurotransmitters in male and female rats: some new observations. *Indian J. Physiol. Pharmacol.* 39, 223–230
39 Mello, N.K. and Mendelson, J.H. (2002) Cocaine, hormones, and behavior: clinical and preclinical studies. *Hormones Brain Behav.* 5, 665–745
40 D'Souza, D.N. *et al.* (1999) Sexual dimorphism in the response to N-methyl-D-Aspartate receptor antagonists and morphine on behavior and c-Fos induction in the rat brain. *Neuroscience* 93, 1539–1547
41 Mozley, L.H. *et al.* (2001) Striatal dopamine transporters and cognitive functioning in healthy men and women. *Am. J. Psychiatry* 158, 1492–1499
42 Staley, J.K. *et al.* (2001) Sex differences in [123I]beta-CIT SPECT measures of dopamine and serotonin transporter availability in healthy smokers and nonsmokers. *Synapse* 41, 275–285
43 Hu, M. *et al.* (2004) Biological basis of sex differences in the propensity to self-administer cocaine. *Neuropsychopharmacology* 29, 81–85
44 Lynch, W.J. *et al.* (2000) Effects of sex and the estrous cycle on regulation of intravenously self-administered cocaine in rats. *Psychopharmacology (Berl.)* 152, 132–139
45 Kemnitz, J.W. *et al.* (1989) Effects of ovarian hormones on eating behaviors, body weight, and glucoregulation in rhesus monkeys. *Horm. Behav.* 23, 235–250
46 Alberti-Fidanza, A. *et al.* (1998) Gustatory and food habit changes during the menstrual cycle. *Int. J. Vitam. Nutr. Res.* 68, 149–153

47 Morgan, M.A. and Pfaff, D.W. (2002) Estrogen's effects on activity, anxiety, and fear in two mouse strains. *Behav. Brain Res.* 132, 85–93
48 Sircar, R. and Kim, D. (1999) Female gonadal hormones differentially modulate cocaine-induced behavioral sensitization in Fischer, Lewis, and Spraque-Dawley rats. *J. Pharmacol. Exp. Ther.* 289, 54–65
49 Zavala, A.R. *et al.* (2000) Cocaine-induced behavioral sensitization in the young rat. *Psychopharmacology (Berl.)* 151, 291–298
50 Green, K.L. *et al.* (1999) The influence of menstrual cycle phase on sensitivity to ethanol-like discriminative stimulus effects of GABA(A)-positive modulators. *Pharmacol. Biochem. Behav.* 64, 379–383
51 Crippens, D. *et al.* (1999) Gender differences in blood levels, but not brain levels, of ethanol in rats. *Alcohol. Clin. Exp. Res.* 23, 414–420
52 Russo, S.J. *et al.* (2003) Gonadal Hormones differentially modulate cocaine-induced conditioned place preference in male and female rats. *Neuroscience* 120, 523–533
53 Koob, G.F. (1992) Neural mechanisms of drug reinforcement. *Ann. N. Y. Acad. Sci.* 654, 171–191
54 Morissette, M. and di Paolo, T. (1993) Sex and estrous cycle variations of rat striatal dopamine uptake sites. *Neuroendocrinology* 58, 16–22
55 Cosgrove, K.P. *et al.* (2002) Wheel-running attenuates intravenous cocaine self-administration in rats: sex differences. *Pharmacol. Biochem. Behav.* 73, 663–671
56 Cosgrove, K.P. and Carroll, M.E. (2003) Effects of a nondrug reinforcer (saccharin) on oral self-administration of phencyclidine (PCP) in male and female rhesus monkeys. *Psychopharmacology (Berl.)* 170, 9–16
57 Campbell, U.C. *et al.* (2002) Sex differences in the effect of baclofen on the acquisition of cocaine self-administration in rats. *Drug Alcohol Depend.* 66, 61–69
58 Cosgrove, K.P. and Carroll, M.E. Effects of bremazocine on oral phencyclidine (PCP) self-administration in male and female rhesus monkeys. (in press)
59 Sershen, S.H. *et al.* (1998) Gender differences in kappa-opioid modulation of cocaine-induced behavior and NMDA-evoked dopamine release. *Brain Res.* 801, 67–71