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Influence of estrogen in the acquisition of intravenously self-administered heroin in female rats

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Abstract

Previous research indicates that female rats acquire cocaine and heroin self-administration at a faster rate than male rats, and female rats with endogenous estrogen, or ovariectomized (OVX) rats with estrogen replacement acquire cocaine self-administration more rapidly than female rats with estrogen either surgically or chemically blocked. The purpose of this investigation was to extend the above findings to the acquisition of heroin (0.0075 mg/kg) self-administration in female rats. An automated autoshaping procedure was used to train rats to self-administer heroin. Three groups of female rats were compared: (1) OVX + estradiol benzoate (OVX + EB), (2) OVX + vehicle (OVX + VEH), and (3) sham-operated + vehicle (SH + VEH). Results revealed that OVX + EB rats acquired heroin self-administration in significantly fewer days compared to OVX + VEH rats. Additionally, OVX + EB rats that met the acquisition criteria self-administered a significantly greater number of heroin infusions during the last 5 days of the acquisition period compared to OVX + VEH rats. These results indicate that OVX + EB rats initiate heroin use sooner than OVX + VEH rats and consume greater amounts of heroin during the last 5 days of acquisition compared to OVX + VEH female rats.

Keywords: Acquisition; Heroin; Estradiol; Estrogen; Intravenous; Ovariectomy; Self-administration

1. Introduction

Heroin is a highly addictive drug that is administered by various methods (e.g., injecting, smoking, snorting), and its use causes serious problems for societies worldwide. Prevalence data from 1999 indicated that an estimated 200,000 Americans were current heroin users, and of these users fewer women were reported to use the drug compared to men (NHSDA, 1999). However, the gap between men and women heroin users appears to be decreasing, and it has been suggested that women take less time than men to become addicted to opioids after initial use (Lex, 1991). Specifically, it has been reported that males were more likely than females to have opportunities to use heroin, but were not more likely than females to progress to actual use once an opportunity occurred (Van Etten and Anthony, 1999). Additionally, women have been reported to initiate heroin use at a significantly younger age compared to men (Chen et al., 1998). These results suggest that women may be more vulnerable to the development of heroin addiction compared to men.

Results of laboratory studies also indicate that sex is a variable that plays an important role in vulnerability to drug addiction. Several reports using animal models of drug self-administration revealed that female rats are more vulnerable to the development of drug-seeking behaviors than male rats (Alexander et al., 1978; Donny et al., 2000; Heppner et al., 1986; Klein et al., 1997; Lancaster and Spiegel, 1992; Morse et al., 1993). Specifically, female rats have self-administered significantly more cocaine (Morse et al., 1993), caffeine (Heppner et al., 1986), morphine (Alexander et al., 1978), fentanyl (Klein et al., 1997), ethanol (Lancaster and Spiegel, 1992), and nicotine (Donny et al., 2000) than male rats. Additionally, data from this laboratory revealed that drug-naïve female rats initially acquired both cocaine and heroin self-administration at a faster rate compared to male rats (Carroll et al., 2001; Lynch and Carroll, 1999). Female rats (compared to males) also displayed greater escalation from controlled, regulated, cocaine self-administration to uncontrolled, ‘‘binge’’ patterns, or dysregulation

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of cocaine self-administration (Lynch et al., 2000). Females were also more vulnerable than males to the reinstatement of cocaine self-administration after an extinction period (Lynch and Carroll, 2000).

The exact causes underlying sex differences in the vulnerability to drug addiction are under investigation, and the female ovarian hormone estrogen appears to play an important role in the observed differences. Justice and de Wit (1999) examined the influence of estrogen and progesterone on subjective responses to D-amphetamine in humans. The results indicated that several positive subjective effects of D-amphetamine were enhanced during the follicular phase relative to the luteal phase of the menstrual cycle. During the follicular phase, estrogen levels are low at first and moderate later, and progesterone levels are low. During the luteal phase, estrogen levels are moderate, and progesterone levels are high. Additionally, Justice and de Wit (1999) reported that positive responses to D-amphetamine were related to high physiological levels of estrogen during the follicular phase, but not the luteal phase. These data suggest that estrogen may enhance the subjective responses to stimulant drugs in women, and that these effects may be antagonized by the presence of progesterone (Justice and de Wit, 1999). Estrogen plays an important role in the sex differences observed in animal models of drug self-administration. It has been reported that the estrous cycle influences a rat's motivation to self-administer cocaine. Specifically, under a progressive ratio schedule, where the number of lever responses required to earn an injection of cocaine is systematically increased after each reinforcement until the animal fails to meet the demands of the schedule, female rats in the estrus phase reach higher breaking points (final ratio completed) compared to both male rats and female rats in other phases of their estrous cycle (e.g., proestrus, metestrus, diestrus) (Roberts et al., 1989). Additionally, Lynch et al. (2001) reported that a greater percentage of ovariectomized (OVX) female rats receiving estrogen replacement (estradiol benzoate, EB) and intact female rats acquired cocaine self-administration compared to female rats with estrogen either surgically (OVX), or chemically blocked with the antiestrogen tamoxifen.

There are fewer reports on the role of estrogen in the self-administration of opioids. Stewart et al. (1996) examined the influence of ovarian hormones (e.g., estrogen and progesterone) on the initiation and maintenance of heroin self-administration in female rats. The results from this study indicated that ovarian hormones had no influence on either component of heroin self-administration in the animals; however, the procedure used to examine the initiation of heroin self-administration included relatively high doses of drug and long periods of access to drug self-administration (Stewart et al., 1996). Therefore, their acquisition procedure may have been insensitive to detecting group differences during this phase of drug self-administration. Sex and hormonal differences are mainly apparent in laboratory animals when low self-administration drug doses are used and during transition states of drug addiction (e.g., acquisition, regulation to dysregulation, and relapse).

The purpose of the present experiment was to examine the role of estrogen in the acquisition of intravenously self-administered heroin in female rats. The acquisition procedure that was used has previously been reported to be a sensitive measure for detecting sex and hormonal differences in rats (Lynch and Carroll, 1999; Lynch et al., 2001). A relatively low dose of heroin (0.0075 mg/kg) and limited access to self-administration were used in order to prevent ceiling effects. Three groups of female rats were compared: (1) OVX + EB, (2) OVX + vehicle (OVX + VEH), and (3) sham-operated + vehicle (SH + VEH). It was hypothesized that OVX + EB and SH + VEH rats would acquire heroin self-administration at a faster rate than OVX + VEH rats, and that the OVX + EB and SH + VEH rats that acquired heroin self-administration would self-administer greater amounts of heroin compared to OVX + VEH rats.

2. Method

2.1. Animals

Twenty-nine sexually mature, female Wistar (Harlan Sprague–Dawley) rats, weighing approximately 250–300 g at the beginning of the experiment, were used as subjects. Initially, rats were individually housed for a minimum of 5 days in hanging stainless steel home cages with free access to food and water. After the acclimation period, each rat was implanted with a chronic indwelling cannula into the right jugular vein, and each rat received either bilateral ovariectomy (OVX) or sham surgery (SH). Following cannulation, the rats were placed in individual test chambers where they remained for the duration of the experiment and were on a 12/12-h light/dark cycle with lights on at 0700 h. Rats had unlimited access to ground Purina Laboratory Chow (Purina Mills, Minneapolis, MN) and water. Food and water were changed daily at 8:00 a.m., and the intake of each was recorded. The experimental protocol was approved by the University of Minnesota Institutional Care and Use Committee under protocol number 9904A00343. Laboratory facilities were accredited by the American Association for the Accreditation of Laboratory Animal Care, and experiments were conducted in accordance with the Principles of Laboratory Animal Care (National Research Council, 1996).

2.2. Apparatus

Experimental test chambers were octagonally shaped with alternating Plexiglas and stainless-steel walls that contained a drinking spout, a recessed food jar, and two response levers (Coulbourn Instruments, Lehigh Valley, PA). A standard light panel consisting of three colored stimulus lights (Coulbourn Instruments) was located above each lever. All three

lights were illuminated during the session except during an infusion. Additionally, a constantly illuminated house light (4.76 W) was located at the top of the chamber. Each chamber was enclosed in a sound-attenuating wooden box that contained a fan for ventilation. An infusion pump (RHSYOCKC, Fluid Metering, Oyster Bay, NY) was mounted outside the chamber and attached to a 500-ml reservoir mounted outside the chamber containing the drug solution. The reservoir was equipped with Tygon tubing (1.52 mm od, 0.51 mm id, Fisher Scientific, Springfield, NJ) that connected to a swivel (050-0022, Alice King Chatham, Hawthorne, CA) mounted at the top of the chamber. A tether (C313CS, Plastic Products, Roanoke, VA) was attached to the swivel and to the rat by a metal cannula (C3236, Plastic One, Roanoke, VA) that was embedded in the center of a plastic covalence-infusion harness (Instech Laboratories, Plymouth Meeting, PA). The indwelling cannula in the rat was attached to the metal cannula embedded in the harness. An IBM-compatible computer with Med-PC interface (Med Associates, St. Albans, VT) was used for programming, data collection, and storage.

2.3. Drugs

Heroin (3,6-diacetylmorphine) HCl was provided by the National Institute on Drug Abuse (Research Triangle Institute, Research Triangle Park, NC) and was dissolved in sterile saline solution. Heroin infusions (0.0075 mg/kg) were delivered at a rate of 0.025 ml/s and the infusion duration was 1 s/100 g of body weight. Infusion durations ranged from 2.5 to 3.0 s, and volumes ranged from 0.06 to 0.075 ml. Heroin solutions were made weekly and stored in 500-ml reservoirs covered with aluminum foil outside each test chamber. The peanut oil (VEH) and 17β-EB were purchased from Sigma-Aldrich (St. Louis, MO), and EB (0.0006 g/ml) was dissolved in peanut oil and injected subcutaneously. This dosing procedure using 0.05 mg/kg for EB has previously been shown to reinstate sexual receptivity in OVX rats (Pfaus and Pfaff, 1992).

2.4. Procedure

Rats were anesthetized with ketamine (90 mg/kg) and pentobarbital (10 mg/kg) prior to cannula implantation. Subsequently, a silicon cannula was inserted into the right jugular vein of each rat following methods that have been previously described (Carroll and Boe, 1982; Lynch et al., 2000; Weeks, 1972). The free tip of the cannula was inserted subcutaneously through an incision approximately 1 cm caudal to the scapulae and, from there, it was connected to a metal cannula embedded in the center of the plastic harness. The day after surgery the tether system was attached to the metal cannula of the plastic harness. OVX and SH surgeries were performed via bilateral dorsal incisions the same day as the cannulation. Subjects were distributed into three groups: (1) OVX + EB ($n = 8$), (2) OVX + VEH ($n = 11$), and (3) SH + VEH ($n = 10$). Beginning 3 days after surgery, rats were given daily (at 8:30 a.m.) subcutaneous injections of EB (0.05 mg/kg) or equal volume VEH. Estrogen has previously been shown to temporarily affect feeding behavior (Tarttelin and Gorski, 1973). Additionally, Eckel and Geary (1999) reported that food intake and meal size were reduced in female rats during estrus, when estrogen levels have peaked and begin to rapidly decline, compared to other phases of the estrous cycle (Eckel and Geary, 1999). Therefore, the acquisition procedure began 7 days after the first pretreatment to allow food intake to stabilize.

The autoshaping procedure used in the present experiment has been previously reported to be sensitive to a number of experimental manipulations (Campbell and Carroll, 2000), and it has been used to detect sex and hormonal differences during the acquisition of drug self-administration (Lynch and Carroll, 1999; Lynch et al., 2001). Daily autoshaping sessions began at 9:00 a.m. and consisted of six 1-h autoshaping components followed by a 6-h self-administration component. At the beginning of each hour of autoshaping three stimulus lights above the retractable and the inactive levers were illuminated. The retractable lever extended five times into the test chamber on a random interval schedule with a mean of 480 s. The lever was retracted after the rat emitted a response on the lever or after 15 s, whichever occurred first. An infusion of heroin was delivered 1 s after each lever retraction. The inactive lever remained extended into the chamber throughout the experiment. Lever presses on the inactive lever were recorded, but not reinforced. Following the five heroin infusions, there was a timeout period for the remainder of the hour. The lever remained retracted, stimulus lights were extinguished, and lever presses were not counted or reinforced. Thus, over the 6-h autoshaping component, a total of 30 (five per hour) heroin (0.0075 mg/kg) infusions were automatically delivered.

During the 6-h self-administration component, the lever remained extended into the test chamber, and the stimulus lights above the levers were illuminated every time the levers were pressed. An active lever press resulted in an infusion of heroin. A 12-h timeout occurred at the end of the 6-h self-administration component. All stimulus lights were extinguished, and responding had no consequences until the beginning of the next day's session. Sessions were run 7 days a week.

The criteria for acquisition of heroin self-administration was a mean of 40 or more infusions during the 6-h self-administration component over five consecutive sessions, or a total of 200 or more infusions within 5 days. If the acquisition criteria were not met within 30 sessions, the experiment was terminated. Every 7 days, rats were weighed and the patency of their cannulas were tested using sodium methohexital (5.0 mg/kg, iv). Patency was assumed if loss of the righting reflex occurred immediately after the injection.

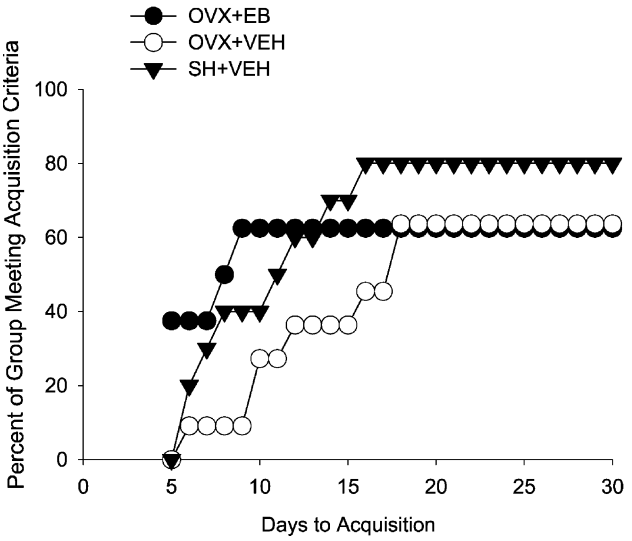

Fig. 1. The percentage of each group of rats to meet the heroin (0.0075 mg/kg) acquisition criteria within the 30-day limit. Data are presented as a function of the 30-day autoshaping testing period. OVX + EB (filled circles) rats acquired heroin self-administration in significantly fewer days than the OVX + VEH (open circles) rats.

Rats were vaginally swabbed daily at 2:30 p.m. to confirm that the structure of their vaginal cells was appropriate for the phase(s) of the estrous cycle that corresponded to their treatment group (e.g., OVX + EB swabs containing proestrus–estrus-like cells, OVX + VEH swabs containing metestrus–diestrus-like cells, SH + VEH swabs containing daily fluctuations in all four types of cells). Swabbing began 7 days prior to self-administration in order to acclimate rats to the procedure. After the acclimation period, swabs were placed on slides, stained with methylene blue, coverslipped, and examined under light microscopy. The metestrus and diestrus phases of the estrous cycle were categorized together and were characterized by few cells, the presence of leukocytes, and necrotic epithelia. Proestrus and estrus phases were categorized separately and were characterized by the presence of predominantly nucleated epithelial cells and predominantly nonnucleated cornified epithelial cells, respectively.

2.5. Data analysis

Dependent measures were the number of days to meet the acquisition criteria, the percentage of rats per group to meet acquisition criteria, drug intake during the 6-h self-administration components over the last five self-administration sessions of the acquisition period, and food and water intake. A one-way analysis of variance (ANOVA) was used to determine the effect of treatment condition on rate of acquisition of heroin self-administration. The Fisher's Least Significant Difference (LSD) test was used for post hoc analysis. Separate two-tailed Student's t tests were used for a priori group comparisons. A value of $P < .05$ determined statistical significance.

3. Results

In Fig. 1, the percentages of each group of rats that met the acquisition criteria for heroin self-administration are presented. Five out of eight (62.5%) of the OVX + EB rats, 7 out of 11 (63.4%) of the OVX + VEH rats, and 8 out of 10 (80%) of the SH + VEH rats met the acquisition criteria for heroin self-administration. The mean number of days to meet the acquisition criteria was 10.0 ± 1.3 (SH + VEH), 12.9 ± 1.7 (OVX + VEH), and 6.4 ± 0.9 (OVX + EB) for the three groups as indicated in parentheses. A one-way ANOVA revealed a significant main effect of treatment condition [$F(2,19) = 4.240$, $P < .05$] on the rate of acquisition. Specifically, OVX + EB rats met the acquisition criteria for heroin self-administration in significantly fewer days compared to the OVX + VEH rats [$F(2,19) = -6.457$, $P < .05$].

Fig. 2 represents the mean number of heroin infusions administered during the last 5 days of the acquisition period for rats in each treatment group that met the acquisition criteria. Two-tailed Student's t tests revealed that OVX + EB rats self-administered significantly more heroin infusions compared to OVX + VEH [$t(58) = 2.256$, $P < .05$] rats. Responses on the inactive lever were low during the 6-h self-administration components of the acquisition procedure, and they did not differ significantly between treatment groups. Between-group comparisons revealed no significant differences regarding food or water intake (data not shown).

Data obtained from vaginal swabbing confirmed that rats were in the phase(s) of the estrous cycle that corresponded with their treatment condition. Specifically, smears obtained from OVX + EB rats consisted predominantly of proestrus–estrus-like cells, while smears obtained from OVX + VEH

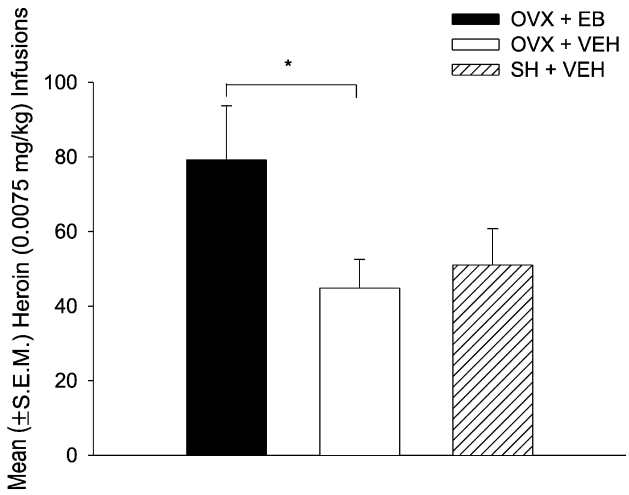

Fig. 2. Mean (±S.E.M.) total number of heroin (0.0075 mg/kg) infusions for each group of rats during the last 5 days of the acquisition period for rats that met the acquisition criteria. There were 5 out of 8 (62.5%), 7 out of 11 (63.4%), and 8 out of 10 (80%) rats that met the acquisition criteria in the OVX + EB, OVX + VEH and SH + VEH groups, respectively. * Groups were significantly different than OVX + VEH rats.

rats consisted predominantly of metestrus–diestrus-like cells. Data obtained from SH + VEH rats confirmed that these animals were cycling completely through all four estrous cycle phases approximately every 3–5 days throughout the entire experiment. One-way ANOVAs were conducted on the SH + VEH group in order to determine if phase of the estrous cycle affected the number of days to acquisition and/or number of heroin infusions self-administered. Results revealed no significant main effect for phase of the estrous cycle on either days to acquisition or number of heroin infusions self-administered (data not shown).

4. Discussion

The results from the present experiment demonstrate that OVX + EB rats acquired intravenously heroin self-administration at a faster rate than OVX + VEH rats. Additionally, the OVX + EB rats that acquired self-administration responded for significantly more infusions of heroin during the last 5 days of the acquisition period compared to OVX female rats treated daily with VEH. These results indicate that surgically blocking ovarian hormones (OVX) in female rats increases the time to acquisition of heroin self-administration, and this delay in acquisition is reversed in OVX + EB rats.

It was hypothesized that the OVX + EB and SH + VEH rats would both acquire heroin self-administration at a faster rate than OVX + VEH rats; however, the results revealed that only the OVX + EB rats acquired heroin self-administration at a faster rate than OVX + VEH rats. This hypothesis was based on results previously reported from this laboratory, which revealed that intact female rats acquired intravenous heroin self-administration at a faster rate than male rats (Carroll et al., 2001; Lynch and Carroll, 1999) and that OVX + VEH female rats displayed cocaine-maintained behavior similar to that of male rats (Lynch et al., 2001). It is unclear why SH + VEH rats from the present study failed to display a significant increase in the rate of acquisition for heroin self-administration compared to OVX + VEH rats. Lynch and Carroll (1999) reported that female rats acquired 0.015 mg/kg heroin self-administration at a significantly faster rate compared to male rats (8.7 days vs. 13 days, respectively); however, the percentages of both females and males that acquired heroin self-administration were high (90% and 91.7%, respectively), and by Day 23 of the 30-day acquisition procedure, female and male rats did not differ in their rates of acquisition. In the present study, a lower dose of heroin (0.0075 mg/kg) was used to avoid ceiling effects. The OVX + EB rats in the present study that acquired heroin self-administration did so at a slightly faster rate than females in Lynch and Carroll's (1999) study (6.4 vs. 8.7 days, respectively). Conversely, as was expected, SH + VEH rats took a slightly longer time to acquire 0.0075 mg/kg heroin self-administration compared to the females that had access to a larger dose of heroin (0.015 mg/kg) in the previous study (10 vs. 8.7 days, respectively) (Lynch and Carroll, 1999).

One explanation for these results may be that EB was administered daily in OVX rats via subcutaneous injections. Daily injections were designed to keep the animals in the proestrus/estrus phase of their estrous cycle. When intact female rats are in this period of their estrous cycle, they have been reported to display increased levels of responding for drugs during the maintenance phase of drug addiction (Roberts et al., 1989; Lynch et al., 2000); therefore, OVX + EB rats may have been more sensitive to the reinforcing effects of heroin compared to SH + VEH rats due to the fact that they were chronically exposed to high levels of estrogen vs. daily fluctuations in estrogen levels (SH + VEH). This may have resulted in the rapid rate to acquisition and increased amount of heroin self-administered in OVX + EB rats. Phase of the estrous cycle did not significantly affect the rate to acquisition or amount of heroin self-administered in SH + VEH rats. However, all of the rats in this group rapidly acquired heroin self-administration, and possibly there was a ceiling effect that occluded differences due to phase of estrous. Alternatively, the rapid fluctuations in estrous phases may not have allowed enough time to detect any effect of phase of the estrous cycle on the rate of acquisition. Additionally, the acquisition of drug self-administration is short-lived, and this feature taken together with rapid daily fluctuations in estrogen levels in SH + VEH rats may have occluded the hypothesized group differences between this group and the OVX + VEH group. It may be useful to use estradiol capsule implants in future studies in order to expose the animals to a sustained hormonal (estradiol) elevation.

The effects of estrogen on heroin self-administration may be different from those that have been reported regarding psychostimulant (e.g., cocaine, amphetamine) self-administration (Lynch et al., 2000, 2001). It is generally accepted that estrogen interacts with the mesolimbic dopaminergic system (Becker, 1999; Thompson and Moss, 1994), which is hypothesized to be the mechanism through which many drugs of abuse mediate their reinforcing effects (DiChiara and Imperato, 1988). It is clear that estrogen's interactions with the striatal and mesolimbic dopaminergic systems are important for both psychostimulant-induced behaviors and psychostimulant self-administration in female rats (Becker, 1990; Lynch et al., 2000; Peris et al., 1991; Sell et al., 2000); however, it is unclear how estrogen may interact with opioid receptors in regions of the central nervous system that are implicated in drug reinforcement.

The results from this study indicate that daily EB treatment increases OVX rats' vulnerability to initiate heroin self-administration compared to OVX + VEH rats. Additionally, daily EB treatment increased the amount of heroin self-administered in OVX female rats that acquired heroin self-administration compared to OVX + VEH rats that acquired self-administration. Therefore, it is possible

that estrogen plays an important role in females' increased vulnerability to self-administer heroin and other opioids. Future research is necessary in order to determine the exact mechanism(s) of estrogen's action on the opioid system and other neurotransmitter systems that are important in drug reinforcement in the brain.

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References

Alexander BK, Coambs RB, Hadaway PF. The effect of housing and gender on morphine self-administration in rats. Psychopharmacology 1978;58: 175–9.

Becker JB. Estrogen rapidly potentiates amphetamine-induced striatal dopamine release and rotational behavior during microdialysis. Neurosci Lett 1990;118:169–71.

Becker JB. Gender differences in dopaminergic function in striatum and nucleus accumbens. Pharmacol, Biochem Behav 1999;64:803–12.

Campbell UC, Carroll ME. Acquisition of drug self-administration: environmental and pharmacological interventions. Exp Clin Psychopharmacol 2000;8:312–25.

Carroll ME, Boe IN. Increased intravenous drug self-administration during deprivation of other reinforcers. Pharmacol, Biochem Behav 1982;80: 65–72.

Carroll ME, Campbell UC, Heideman P. Ketoconazole suppresses food restriction-induced increases in heroin self-administration in rats: sex differences. Exp Clin Psychopharmacol. 2001;9:307–16.

Chen CK, Shu LW, Liang PL, Hung TM, Lin SK. Drug use patterns and gender differences among heroin addicts hospitalized for detoxification. Changgeng Yi Xue Zhi 1998;21:172–8.

Di Chiara G, Imperato A. Drugs abused by humans preferentially increase synaptic dopamine concentrations in the mesolimbic system of freely moving rats. Proc Natl Acad Sci 1988;85:5274–8.

Donny EC, Caggiula AR, Rowell PP, Gharib MA, Maldovan V, Booth S, Mielke MM, Hoffman A, McCallum S. Nicotine self-administration in rats: estrous cycle effects, sex differences and nicotinic receptor binding. Psychopharmacology 2000;151:392–405.

Eckel LA, Geary N. Endogenous cholecystokinin's satiating action increases during estrus in female rats. Peptides 1999;20:451–6.

Heppner CC, Kemble ED, Cox MW. Effects of food deprivation on caffeine consumption in male and female rats. Pharmacol, Biochem Behav 1986; 24:1555–9.

Justice AJ, de Wit H. Acute effects of D-amphetamine during the follicular and luteal phases of the menstrual cycle in women. Psychopharmacology 1999;145:67–75.

Klein LC, Popke JE, Grunberg NE. Sex differences in effects of predictable and unpredictable footshock on fentanyl self-administration in rats. Exp Clin Psychopharmacol 1997;5:99–106.

Lancaster FE, Spiegel KS. Sex differences in pattern of drinking. Alcohol 1992;9:415–20.

Lex B. Gender differences and substance abuse. Adv Subst Abuse 1991;4: 225–96.

Lynch WJ, Carroll ME. Sex differences in the acquisition of intravenously self-administered cocaine and heroin in rats. Psychopharmacology 1999;144:77–82.

Lynch WJ, Carroll ME. Reinstatement of cocaine self-administration in rats: sex differences. Psychopharmacology 2000;148:196–200.

Lynch WJ, Arizzi MN, Carroll ME. Effects of sex and the estrous cycle on regulation of intravenously self-administered cocaine in rats. Psychopharmacology 2000;152:132–9.

Lynch WJ, Roth ME, Mickelberg JL, Carroll ME. Role of estrogen in the acquisition of intravenously self-administered cocaine in female rats. Pharmacol, Biochem Behav 2001;68:641–6.

Morse AC, Erwin VG, Jones BC. Strain and housing affect cocaine self-selection and open-field locomotor activity in mice. Pharmacol, Biochem Behav 1993;45:905–12.

National Household Survey on Drug Abuse (NHSDA). National estimates of substance use. 1999. Available at: http://www.samhsa.gov/oas/NHSDA/1999/Chapter2.htm.

National Research Council. Guide for the care and use of laboratory animals. Washington (DC): National Academy Press, 1996.

Peris J, Decambre CH, Coleman-Hardee ML, Simpkins JW. Estradiol enhances behavioral sensitization to cocaine and amphetamine-stimulated striatal [H^3]dopamine release. Brain Res 1991;566:255–64.

Pfaus JG, Pfaff DW. Mu, delta, and kappa opioid receptor agonists selectively modulate sexual behaviors in the female rat: differential dependence on progesterone. Horm Behav 1992;26:457–72.

Roberts DCS, Bennett SAL, Vickers GJ. The estrous cycle affects cocaine self-administration on a progressive ratio schedule in rats. Psychopharmacology 1989;98:408–11.

Sell SL, Scalzitti JM, Thomas ML, Cunningham KA. Influence of ovarian hormones and estrous cycle on the behavioral response to cocaine in female rats. J Pharmacol Exp Ther 2000;293:879–86.

Stewart J, Woodside B, Shaham Y. Ovarian hormones do not affect the initiation and maintenance of intravenous self-administration of heroin in the female rat. Psychobiology 1996;24:154–9.

Tarttelin MF, Gorski RA. The effects of ovarian steroids on food and water intake and body weight in the female rat. Acta Endocrinol 1973;72: 551–68.

Thompson TL, Moss RL. Estrogen regulation of dopamine release in the nucleus accumbens: genomic- and nongenomic-mediated effects. J Neurochem 1994;62:1750–6.

Van Etten ML, Anthony JC. Comparative epidemiology of initial drug opportunities and transitions to first use: marijuana, cocaine, hallucinogens and heroin. Drug Alcohol Depend 1999;54:117–25.

Weeks JR. Long-term intravenous infusion. In: Myers RD, editor. Methods in psychobiology. London: Academic Press, 1972. pp. 155–68.