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ORIGINAL INVESTIGATION

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Intravenous cocaine and heroin self-administration in rats selectively bred for differential saccharin intake: phenotype and sex differences

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Abstract *Rationale:* Rats selectively bred for high intake of a sweet saccharin solution (HiS) consume more ethanol than their low-saccharin intake (LoS) counterparts. The HiS phenotype may be a predictor of abuse of other drugs via other routes of administration. *Objective:* HiS and LoS, male and female rats were tested for acquisition of IV cocaine and heroin self-administration under a fixed-ratio 1 (FR1) schedule, and cocaine-reinforced behavior was examined under a progressive-ratio (PR) schedule. *Methods:* Four groups of rats (HiS males and females and LoS males and females) were trained to self-administer IV cocaine (0.2 mg/kg), and another four groups were trained to self-administer heroin (0.015 mg/kg) using an automated autoshaping procedure. Rats were allowed 30 days to reach a criterion whereby a mean of 100 (cocaine) or 20 (heroin) infusions were self-administered during 6-h sessions over 5 consecutive days. *Results:* The HiS female rats acquired cocaine self-administration significantly more rapidly than the LoS rats, and females of both phenotypes met the acquisition criteria more rapidly than males. In both HiS and LoS cocaine groups a greater percentage of females (compared with males) met the acquisition criteria within 30 days. The only cocaine group in which 100% met the criterion was the HiS females. The female (compared with male) heroin groups showed a more rapid rate of acquisition, but there was no difference due to saccharin phenotype. In each of the four heroin groups 100% of all rats met the criteria within 30 days. Results of the PR schedule in the HiS females and males and LoS females indicated significantly higher break points in the HiS females (compared with HiS males), but there were no differences in females due to phenotype. *Conclusion:* Female rats selectively bred for higher saccharin intake show more rapid and successful acquisition of IV self-administration of a low dose of cocaine than those bred for low saccharin intake. Female rats (compared with males) consistently showed accelerated rates of acquisition and maintenance (PR) of cocaine self-administration and acquisition of heroin self-administration.

Keywords Acquisition · Autoshaping · Breeding · Cocaine · Heroin · Intravenous · Phenotype · Rat · Saccharin · Selective · Sex

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Introduction

A number of factors have been identified in recent years that correlate with and predict vulnerability to drug abuse. For example, rats selected for higher activity levels (Piazza et al. 1989, 2000; Piazza and LeMoal 1996, 1998; Pierre and Vezina 1997; Rhodes et al. 2001; Suto et al. 2001) and reactivity (Pothos et al. 1995) show enhanced locomotor and reinforcing effects of drugs compared to their counterparts with lower activity levels. Similarly, rats selected for having greater avidity for sweet tastes more rapidly acquire amphetamine (De Sousa et al. 2000), ethanol (Bell et al. 1994; Gahtan et al. 1995; Gosnell and Krahn 1992), and morphine (Gosnell et al. 1995) self-administration than those with lower sweet preferences. The activity and consummatory behaviors and elevated drug self-administration, have been linked to mesolimbic dopaminergic (Piazza et al. 1991a, 1991b; Carr and Kutchukidze 2000) and opioid (Werme et al. 2000; Lett et al. 2001; Zhang and Kelley 2002) mechanisms. Concordant findings from human studies illustrate the correlative effects of alcohol and

drug abuse and activity (Alessi et al. 2000) as well as taste sensitivity and avidity for sweets (Morabia et al. 1989; Willenbring et al. 1989; Yamamoto et al. 1991; Pelchat and Danowski 1992; Kampov-Polevoy et al. 1995a, 1995b, 1997, 1999, 2001; Hirsch 1997; Carroll 1999).

Animals that are selectively bred for high or low activity or reactivity (Adams et al. 1991; Overstreet et al. 1993; Haney et al. 1994; Cools and Gingras 1998; West et al. 1999) and intake of sweet liquids (Dess et al. 1998) are also more sensitive to the locomotor and reinforcing effects of drugs of abuse. A goal of the present research was to compare rats from Occidental College (Los Angeles, Calif., USA) that were selectively bred for high (HiS) and low (LoS) saccharin consumption (Badia-Elder et al. 1996; Dess and Minor 1996; Dess et al. 1998) on the acquisition of IV cocaine and heroin self-administration. Cocaine self-administration under a progressive ratio (PR) schedule was also evaluated under limited conditions.

Selective breeding is not only useful to identify correlates of the selection phenotype and behavioral variables (e.g. sweet preference and elevated drug effects), but other correlates may be revealed that serve as markers for drug abuse. For example, selection for ethanol (Sinclair et al. 1992; Overstreet et al. 1993) or saccharin (Dess et al. 1998) has correlates with ingestive behavior (sweet or drug intake, respectively). In fact, the characteristic that has been selectively bred may be a general tendency to consume flavored solutions. Differences in emotionality and pain sensitivity have also been linked to ethanol (Badistov et al. 1995; Kampov-Polevoy et al. 1996; Overstreet et al. 1997) and saccharin (Dess and Minor 1996; Dess et al. 2000) consumption. There is clearly a genetic influence in bitter and sweet taste sensitivity in humans (Bartoshuk 1979; Gent and Bartoshuk 1983; Bartoshuk et al. 1988; Looy and Weingarten 1992), and its relationship to drug abuse (Pelchat and Danowski 1992).

Comparisons of male and female rats in recent studies of the acquisition (Lynch and Carroll 1999; Carroll et al. 2001), maintenance (Lynch and Carroll 1999), regulation (Lynch et al. 2000) and reinstatement of drug-seeking behavior after an extinction period (Lynch and Carroll 2000), have consistently shown that females exceed males during all of these phases of drug-seeking behavior (Lynch WJ et al., unpublished data). Female rats (Campbell et al. 2002; Carroll et al. 2001; Cosgrove KP, Carroll ME, unpublished data) and rhesus monkeys (Cosgrove KP et al., unpublished data; Cosgrove KP, Carroll ME, unpublished data) are also affected more than males by behavioral and pharmacological treatments. The elevated self-administration levels in females are related to the presence of estrogen (Lynch et al. 2001, and unpublished data; Roth et al. 2002). In contrast, there are also reports of no sex differences (Stewart et al. 1996) or hormonal effects on the acquisition of drug self-administration. Thus, another goal of this investigation was to compare males and females from the HiS and LoS groups to determine whether sex differences exist within the different saccharin consumption phenotypes.

In the present experiment, acquisition of IV cocaine and heroin self-administration was compared in rats bred for high (HiS) and low (LoS) saccharin intake by Dess and colleagues (Badia-Elder et al. 1996; Dess and Minor 1996; Dess et al. 1998). Subsequently, a progressive ratio (PR) schedule developed to assess the reinforcing efficacy of cocaine self-administration (Roberts et al. 1989) was used to compare reinforcing efficacy of cocaine as a function of the saccharin intake phenotype and sex once self-administration behavior had stabilized.

Materials and methods

Animals

Seventy experimentally naive, Sprague-Dawley rats (34 female, 36 male) were bred from litters selected for high (HiS) and low (LoS) scores for saccharin intake during a 24-h two-bottle test with 0.1% (w/v) sodium saccharin and water. The Occidental HiS and LoS rats used in the present study were derived from the only existing lines that are based on a saccharin-intake phenotype (Dess et al. 1998). The line originated in 1990 from an avid saccharin-drinking male paired with several females that were unremarkable for their saccharin drinking. Subsequent generations of HiS and LoS rats resulted from pairing extreme HiS males with HiS females and LoS males with LoS females from different litters without mating siblings, half-siblings, or cousins. A small number of founders from the parental stock (Holtzman, HSD from Harlan Sprague-Dawley, Inc. Indianapolis, Ind., USA) have been added to the breeding program every four or five generations to maintain their vigor. Dess and co-workers derived a saccharin consumption phenotype score from a 24-h test with saccharin (0.1% w/v) and water available. The amount of saccharin consumed was compared with average 24-h water intake during the last 5 days of the acquisition period, and the difference in consumption (saccharin-water) was expressed as a percentage of body weight (g). A positive or negative score, respectively, indicated whether saccharin intake was greater (preference) or less than (aversion) the average daily water intake. A zero score indicated no preference or aversion for saccharin compared to water. The HiS and LoS lines diverged on this measure by the third generation, and the 17–20th generations were used in this experiment.

Basic information regarding the sample sizes, body weight, food and water intake, and phenotype scores are shown in Table 1. An original group of 24 rats in the 17–18th generations were obtained from a breeding program conducted at Occidental College, Los Angeles, Calif., USA. Some of those rats were bred according to similar procedures, and the remaining subjects were from generations 19–20 bred in the Minnesota laboratory. Rats were group housed in same-sex pairs in plastic cages until they were used in the experiment. Before and during the acquisition experiment all rats had ad libitum access to food and water. Food intake and body weights were significantly higher in males than females, but the groups did not differ on these measures according to phenotype. Water intake did not vary according to sex or phenotype.

Each rat was implanted with an indwelling catheter in the jugular vein to the level of the right atrium. Subsequently, each rat was placed individually in an operant conditioning chamber, where it lived for the duration of the experiment. All rats were food satiated during the acquisition period, and they were food-restricted to 85% of their free-feeding body weights during the PR schedule. When they were food restricted, males received 20 g and females received 16 g of food per day, amounts that maintained males and females at 85% of free-feeding weights, respectively. Water was available ad libitum throughout the experiment. The

Table 1 Basic information on experimental groups

Group	*n*	Body weight	Mean (+SEM) food intake (g)	Mean (+SEM) water intake	Mean phenotypescore (+SEM)[a]
Cocaine					
HiS F	9	383.4 (6.9)	15.9 (1.9)	32.9 (1.6)	24.4 (3.5)
LoS F	8	348.8 (6.6)	19.5 (1.7)	39.1 (3.4)	13.4 (3.4)
HiS M	6	581.5 (41.5)	22.9 (1.9)	29.2 (3.1)	7.5 (1.3)
LoS	7	523.6 (27.2)	25.4 (1.3)	47.2 (4.0)	–4.3 (2.7)
Heroin					
HiS F	9	363.7 (15.0)	17.8 (1.0)	36.6 (2.2)	31.1 (17.6)
LoS F	11	379.5 (8.6)	21.1 (0.9)	39.3 (3.8)	8.7 (4.4)
HiS M	10	548.0 (14.3)	26.9 (0.7)	45.9 (3.5)	13.5 (3.7)
LoS M	10	492.3 (8.9)	23.4 (1.2)	43.3 (3.0)	2.5 (1.6)

[a] Phenotype score=(saccharin intake–water intake)/body wt×100. Saccharin intake was based on the 24-h measure during the saccharin-water preference test. The water measure used to calculate the phenotype score was the mean water intake during the acquisition period that immediately preceded the saccharin-water preference test. This transformation is the selection phenotype score used to create the Occidental HiS and LoS lines (Dess and Minor 1996)

rooms in which the rats and operant conditioning chambers were housed were controlled for temperature (24°C) and humidity. Use of animals for this protocol was approved by the University of Minnesota Institutional Animal Care and Use Committee (protocol number 9904A00343). Laboratory facilities were accredited by the American Association for the Accreditation of Laboratory Animal Care, and recommended principles of laboratory animal care were followed (National Research Council 1996).

Apparatus

The operant conditioning chambers were octagon-shaped with alternating stainless-steel and Plexiglas walls. On two of the stainless steel walls, a retractable lever and a standard response lever were mounted (Coulbourn Instruments, Allentown, N.J., USA). There were three colored (red, yellow, green) stimulus lights (4.6 W) above each lever, and the experimental chamber was illuminated by a white 4.6 W house light mounted at the top of the chamber. Each operant conditioning chamber was housed in a wooden enclosure for sound attenuation. A ventilation fan added additional white noise. Infusion pumps (model RHSYOCKC, Fluid Metering, Inc. Oyster Bay, N.Y., USA) were mounted on the outside of the wooden enclosures. The indwelling cannula in the rat was connected to a spring-covered connecting cannula by an attachment (C3236, Plastics One, Roanoke, Va., USA) that was embedded in the center of a soft plastic covance-infusion harness (CIH95 Instech Laboratories, Plymouth Meeting, Pa., USA). The rats' infusion tubing was covered by a spring-covered cannula (C313CS, Plastics One, Roanoke, Va., USA), which was attached to a swivel (050-0022, Alice King Chatham, Hawthorne, Calif., USA). The swivel was connected via Tygon tubing (1.52 mm o.d.; 0.51, mm i.d., Fisher Scientific, Springfield, N.J., USA) to the infusion pump. Experiments were programmed, and data were recorded using IBM-compatible computers and MED-PC software (Med Associates, St Albans, Vt., USA).

Procedure

Experimental sessions began 3 days after surgery. Sessions began at 9:00 a.m. each day and were conducted 7 days per week. Between 8:00 and 9:00 a.m. each day food, water and drug solutions were replenished, and intakes were measured. The operant conditioning chambers were cleaned daily. The IV catheter function was checked approximately every 7 days by administering sodium methohexital (5 mg/kg, IV). A subsequent loss of the righting reflex was used as an indicator of catheter patency.

Four groups of rats were trained to self-administer cocaine (0.2 mg/kg), and four groups were trained to self-administer heroin (0.015 mg/kg) according to an autoshaping procedure (Carroll and Lac 1993; Lynch and Carroll 1999; Campbell and Carroll 2000) that is described below (see Table 1 for group sizes). Subsequently, the four cocaine groups were compared under a PR schedule similar to that reported by Roberts and coworkers (1989). As the heroin groups did not differ in the rate of acquisition, they were not compared under a PR schedule.

Acquisition/autoshaping component

At the start of each session, three colored stimulus lights above the retractable and standard levers were illuminated. The retractable lever was extended 10 times each h for the cocaine groups and 5 times each hour for the heroin groups under a random-time 90 s schedule for cocaine and a random time 480 s schedule for heroin. The lever retracted immediately if the animal touched it, or after 15 s, whatever came first. After the lever was retracted, an infusion of cocaine (0.2 mg/kg) or heroin (0.015 mg/kg) was automatically delivered. These random infusions occurred during the first 13–15 min of each hour in the 6-h session for cocaine and during the first 30–35 min of each of the 6 h for heroin (Lynch and Carroll 1999). During the remainder of each h the lever remained retracted, and responding had no programmed consequences. Thus, over the 6-h autoshaping component a total of 60 (10/h) cocaine or 30 (5/h) heroin infusions were delivered under a random-time schedule. Responses on the inactive lever were counted but had no programmed consequences.

Acquisition/self-administration component

Each day a 6-h self-administration component followed the autoshaping component. The retractable lever remained extended, and cocaine or heroin infusions were contingent upon lever pressing under a fixed-ratio 1 (FR1) schedule. Responses that occurred during the infusion and responses on the inactive lever were counted, but they had no programmed consequences. At the end of the 6-h self-administration component there was a 12-h time-out period until the next session began at 9:00 a.m. the next day. The acquisition criterion for cocaine was a mean of at least 100 infusions per day for five consecutive self-administration components, which was the criterion used previously (Carroll and Lac 1993, 1997, 1998; Lynch and Carroll 1999). For heroin, the criterion was a mean of 20 infusions per day for 5 consecutive days, as reported by Lynch and Carroll (1999).

Progressive-ratio (PR) phase

The animals that met the cocaine acquisition criterion were subsequently placed under an FR1 schedule during 6-h sessions (9 a.m. to 3 p.m.) until behavior stabilized. They were then tested with a PR schedule with 0.2 mg/kg cocaine for 3–5 days. The heroin groups were not tested under the PR schedule, as there were no phenotype differences at the end of the acquisition phase, and initial results revealed no differences under the PR. The PR schedule was similar to that described by Roberts and coworkers (1989). The first response during each daily session produced an infusion, and each succeeding infusion was contingent upon a progressively greater number of lever-press responses according to the following series: 2, 4, 6, 9, 12, 16, 20, 28, 36, 48, 63, 83, 110, 145, 191, 251, 331, 437, 575, 759 and 999 (Roberts et al. 1989). The break point was defined as the highest ratio completed by the end of the 6-h session. Mean break points were reported for each rat for the first 3 days when there was a difference of 1 or less between total infusions earned per day.

Drugs

Cocaine and heroin (3,6-diacetylmorphine) HCl were obtained from the National Institute on Drug Abuse (Research Triangle Institute, Research Triangle Park, N.C., USA). Drugs were dissolved in sterile physiological saline, stored in 500 ml reservoirs covered with aluminum foil, and connected to the infusion pumps that were on the outside of the wooden enclosure. Cocaine (0.2 mg/kg) and heroin (0.015 mg/kg) were delivered at a rate of 0.03 ml/s. The infusion duration was 1 s/100 g of body weight (between 3.6 and 5.8 s). For example, the infusion volume was 0.125 ml for a 500 g rat.

Data analysis

Dependent measures were percent of each group meeting the acquisition criterion, mean number of days per group to meet the criterion, and mean number of infusions over the last 5 days before the acquisition criterion was met. Mean break point under the PR schedule, 24-h saccharin and water intake from the last 5 days of the acquisition period, phenotype score for saccharin intake, and mean food and water consumption during the acquisition period were also analyzed. The percentage of rats acquiring cocaine- or heroin-reinforced behavior between the four groups (HiS versus LoS, male versus female) was compared with the Kaplan-Meier survival analysis and the Breslow-Gehan-Wilcoxon statistic (Statview: Abacus Concepts, Berkeley, Calif., USA). Randomized factorial analyses of variance (ANOVA) were conducted to compare the four groups on other dependent measures. Post-hoc comparisons were conducted with Fisher's LSD protected *t*-tests (GB Stat, Dynamic Microsystems, Inc., Silver Spring, Md.). Results were considered statistically significant if $P<0.05$.

Results

Table 1 shows the mean body weights for each group as well as mean food and water intakes during the acquisition period. During the acquisition phase, rats were allowed unlimited access to food and water. Initial body weights did not differ significantly across phenotype in female or male groups in either the cocaine or heroin condition; however; males weighed significantly more than females both in the cocaine ($F=63.6$, $df=1, 26$, $P<0.05$) and heroin ($F=157.4$, $df=1, 36$, $P<0.05$) conditions. During acquisition, water consumption did not significantly differ as a function of sex, phenotype, or drug self-administered. In both the cocaine and heroin groups males consumed more food than the females ($F=9.31$, $df=1, 23$, $P<0.05$ and $F=33.3$, $df=1, 38$, $P<0.05$, respectively); however, there were no significant differences due to phenotype. Finally, for all of the groups there was little or no responding on the inactive lever throughout the experiment (data not shown).

Figure 1 shows the cumulative percent of each group meeting the cocaine (left panel) or heroin (right panel) acquisition criteria over the 30-day testing period. In the cocaine groups the rate of acquisition was higher in the HiS groups (filled symbols) compared to their LoS counterparts (open symbols). For the cocaine groups a survival analysis indicated that this phenotype effect was statistically significant in the females ($\chi^2=11.5$, $df=1$, $P<0.05$) but not in males. A greater percentage of females (versus males) in both the HiS and LoS groups acquired cocaine self-administration. The survival analysis also indicated a significant sex effect in the HiS groups ($\chi^2=4.33$, $df=1$, $P<0.05$) but not in the LoS groups.

In the heroin groups a greater percentage of HiS rats (versus LoS) met the criterion early in acquisition (5–10 days); however, by day 30, 100% of all groups had met the criterion. The survival analyses of the groups self-administering heroin yielded a significant effect in the HiS groups for sex ($\chi^2=4.65$, $df=1$, $P<0.05$)

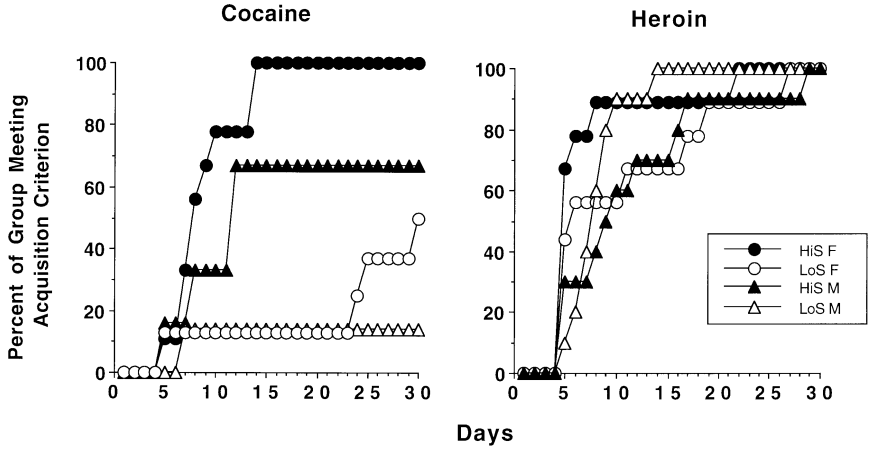

Fig. 1 Cumulative percentage of rats in each group meeting the criteria for acquisition of cocaine (*left panel*) and heroin (*right panel*) self-administration within the 30-day limit. The criterion for cocaine acquisition was mean of 100 infusions and for heroin it was 30 infusions over 5 consecutive days. *Filled circles* refer to HiS F; *open circles* to LoS F; *filled triangles* indicate HiS M, and *open triangles* LoS M groups

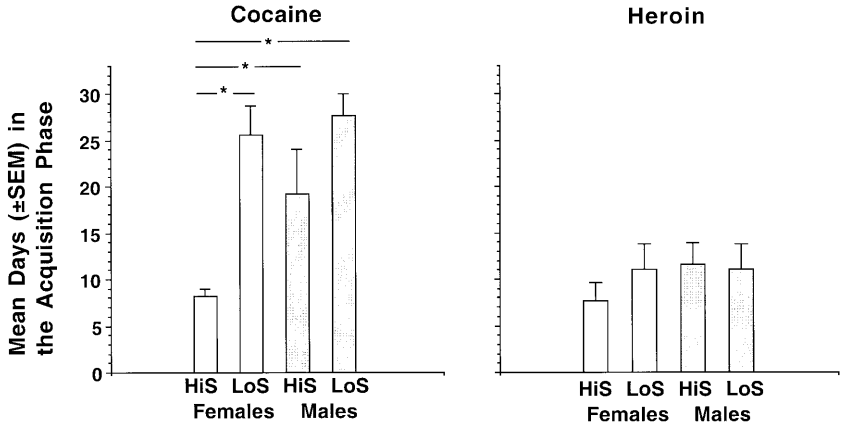

Fig. 2 Mean number of days (±SEM) spent in the 30-day acquisition period for cocaine (*left panel*) and heroin (*right panel)* are presented for the four groups labeled from left to right, HiS F, LoS F, HiS M, LoS M. *Open bars* refer to female rats and *shaded bars* refer to males. Rats that had not met the acquisition criteria (see caption for Fig. 1) by the 30-day limit were assigned a score of 30 days. *Horizontal bars* and *asterisks* designate the paired-comparisons that were significantly different at $P<0.05$

but not for phenotype. Similarly, when the number of infusions for the four heroin groups were compared with an ANOVA on day 5, there was a significant sex effect ($F=7.16$, $df=1,39$, $P<0.05$), with the females self-administering more infusions than males in the HiS group ($t=2.98$, $df=16$, $P<0.05$). Thus, significant phenotype and sex differences in rate of acquisition were revealed in the female cocaine groups, and sex differences occurred in the HiS heroin groups.

Figure 2 shows the mean number of days the rats in each group spent in the acquisition phase. Rats that did not acquire in 30 days were assigned the maximum of 30 days as in previous studies (Carroll and Lac 1993, 1997, 1998; Lynch and Carroll 1999). In the cocaine groups (left panel) the overall ANOVA was significant for phenotype ($F=17.97$, $df=1, 26$, $P<0.05$), but not a significant sex-phenotype interaction indicating that the HiS rats met the acquisition criteria in fewer days than the LoS rats. There was also a significant effect due to sex ($F=4.41$, $df=1, 26$, $P<0.05$), but not a significant interaction. Post-hoc comparisons indicated that there were significant phenotype differences between the HiS F and the LoS F, HiS M and LoS M groups ($t=4.43$, 2.59 and 4.65, respectively). A similar analysis in the heroin groups (right panel) did not result in a significant effect for sex or phenotype. Lack of significant differences in the heroin groups may have resulted from a ceiling effect due to dose, since 100% of the rats in each group met the acquisition criterion.

In Table 2 the mean number of cocaine (left panel) and heroin infusions (right panel) during the last 5 days of acquisition (for rats that met the acquisition criterion) for cocaine and heroin self-administration are compared across sex and phenotype. These were the 5 days in which the acquisition criterion was met. In the cocaine groups there was a gradual increase in infusions over the 5 days. The number of rats meeting the criterion (indicated in parentheses) decreased across groups HiS F (9), LoS F (4), HiS M (3) and LoS M (1). Due to the small number of subjects in some of the cocaine groups, statistical analyses were not conducted. The pattern of acquisition in the heroin groups differed from the cocaine groups in that there were, overall, fewer infusions, and most infusions occurred on the last 2 of the 5 days. All of the heroin groups (right panel) acquired within 30 days ($n=9$, 11, 10 and 10 for the HiS F, LoS F, HiS M and LoS M groups, respectively). Results of a repeated measures ANOVA over the 5 days revealed no significant differences across the four heroin groups. These different patterns of acquisition for cocaine and heroin were similar to those that have been previously reported (Lynch and Carroll 1999).

The data from three groups were compared under the PR schedule, as only 1 rat in the LoS male group acquired cocaine self-administration and completed the PR. Mean break points (left panel) and infusions (right panel) were taken from the last 3 days under the PR schedule. Table 3 shows the break points and numbers of

Table 2 Mean (±SEM) infusions during the last 5 days of acquisition

Days	Females		Males	
Cocaine	HiS ($n=9$)	LoS ($n=9$)	HiS ($n=3$)	LoS ($n=1$)
1	53.2 (23.6)	95.3 (35.4)	43.7 (41.7)	0 (0)
2	87.6 (21.1)	85.8 (45.1)	83.0 (28.4)	130.0 (0)
3	104.1 (27.1)	109.0 (43.1)	126.3 (42.9)	171.0 (0)
4	171.1 (32.9)	219.3 (41.9)	122.0 (20.1)	157.0 (0)
5	249.3 (40.4)	184.8 (49.5)	211.3 (2.4)	172.0 (0)
Heroin	HiS ($n=9$)	LoS ($n=11$)	HiS ($n=10$)	LoS ($n=10$)
1	17.8 (6.4)	17.2 (12.7)	5.5 (1.8)	13.0 (4.8)
2	15.8 (5.6)	12.7 (7.5)	9.6 (3.0)	10.2 (2.3)
3	23.0 (8.8)	42.8 (17.5)	22.9 (6.0)	21.6 (5.1)
4	63.2 (28.8)	56.3 (19.8)	45.0 (17.1)	35.5 (4.8)
5	102.8 (15.2)	95.0 (28.5)	60.5 (8.6)	48.0 (12.4)

Table 3 Progressive ratio data for cocaine groups

Groups	Mean (±SEM) break point	Mean (±SEM) infusions
HiS F ($n=8$)	128.8 (34)	12.59 (1.0)
LoS F ($n=8$)	146.7 (52.3)	12.38 (1.5)
HiS M ($n=3$)	35.2 (11.2)	8.1 (1.1)

Table 4 Saccharin and water intake (±SEM) during the 24-h two-bottle test

Group	Females		Males	
Cocaine	HiS (*n*=9)	LoS (*n*=8)	HiS (*n*=6)	LoS (*n*=7)
Saccharin	129.8 (17.9)	92.2 (12.6)	74.2 (10.5)	50.1 (18.2)
Water	57.5 (5.1)	53.3 (2.4)	41.1 (3.8)	72.4 (2.7)
Heroin	HiS (*n*=9)	LoS (*n*=11)	HiS (*n*=10)	LoS (*n*=10)
Saccharin	150.5 (66.7)	28.5 (24.8)	117 (21.5)	30.9 (9.7)
Water	56.8 (4.1)	57.6 (8.2)	67.5 (4.7)	66.5 (4.1)

infusions for each group. An ANOVA indicated a significant effect due to sex (HiS F versus HiS M) for both break points (t=2.55, df=12, P<0.05) and infusions (t=3.24, df=12, 20, P<0.05), but not phenotype (HiS F versus LoS F). Thus, the PR schedule was not as sensitive to phenotype differences as the acquisition measures. Post hoc analyses indicated that infusions were significantly higher for females than males in the HiS groups (t=2.23, df=11, P<0.05). In both males and females, break points and infusions for the HiS groups were nearly identical indicating that maintenance (PR) measures were less sensitive to phenotype differences than acquisition measures.

After the acquisition and PR measures were obtained, the groups were tested with 24-h two-bottle access to saccharin and water to verify the behavioral phenotypes. Table 4 shows the saccharin intake (in ml) during this 24-h period for the cocaine (left panel) and heroin (right panel) groups. Water intake is also shown, but in accordance with the calculation of the phenotype scores that was used earlier (Dess et al. 1998), mean water intake was derived from the 5-day period that preceded the saccharin-water, two-bottle 24-h test. In both cocaine and heroin conditions there were no significant differences across groups in water intake. The cocaine groups differed significantly in saccharin intake according to sex (F=3.69, df=1, 26, P<0.05). Although the overall phenotype effect just missed statistical significance (P<0.06), planned comparisons of the cocaine groups indicated that the HiS and LoS females were significantly different (P<0.05), and there was also a significant sex difference between the HiS F and HiS M groups (P<0.05). The heroin groups differed according to phenotype (F=14.02, df=1, 29, P<0.05), but not according to sex. Post-hoc comparisons indicated significant differences in saccharin intake between the HiS and LoS groups in both males and females. An ANOVA was also conducted with the transformed phenotype scores, and it yielded significant differences for sex (F=9.67, df=26, P<0.05) and phenotype (F=7.24, df=1,26, P<0.05) for the cocaine groups and for phenotype (F=12.19, df=1,29, P<0.05) but not sex for the heroin groups. Overall, these findings indicate that the phenotype differences in these rats were similar to data from rats from the same breeding lines used in previous work (e.g. Dess 2000), and that the drug self-administration experience that occurred before saccharin testing did not change the rank ordering of the groups on phenotype measures.

Discussion

This experiment showed that HiS female rats acquired cocaine self-administration at a faster rate (fewer days) than those bred for low saccharin intake. Females initiated cocaine self-administration more rapidly than males, and a greater percentage of females than males met the acquisition criterion within 30 days. The percentage of cocaine groups meeting the acquisition criterion from highest to lowest was HiS F (100%), HiS M (66%), LoS F (52%), LoS M (14.3%). All of the heroin rats met the acquisition criterion within 30 days. The heroin groups showed a significant effect of number of days to acquisition for sex (M>F) but not phenotype, except on day 5 the HiS heroin groups exceeded the LoS groups in heroin infusions in both males and females. The present results with female rats and IV cocaine self-administration concur with earlier work with these strains of rats and oral ethanol intake (Dess et al. 1998) indicating that saccharin preference predicts a faster rate and higher probability of acquisition of cocaine self-administration.

The present results are also in agreement with previous research concerning the saccharin phenotype scores, with the scores ordered from highest to lowest for the four groups, respectively: HiS F, LoS F, HiS M, LoS M (Dess 2000). For heroin, the rank order of the LoS F and HiS M scores was reversed; however, the scores of these two middle groups is often similar, and they are consistent with the order of the saccharin scores previously reported for some of the groups tested by Dess (2000). The present saccharin phenotype scores were lower across all four groups compared to previous measures (Dess 2000). The scores ranged from a strong preference (HiS F) to an aversion (LoS M). Phenotype scores are typically obtained after other experimental procedures have been completed to prevent carry-forward effects of saccharin exposure. The lower scores in the present experiment may have been due to carry-forward effects of prior exposure to cocaine and heroin. Also, a reward comparison effect may have occurred, whereby the reward of drug self-administration overshadowed the rewarding effects of saccharin, reducing the value of saccharin. This hypothesis has been applied to the reduced saccharin intake that occurs when drugs of abuse and saccharin are juxtaposed in a taste aversion paradigm (Grigson 1997).

The phenotype effect may not necessarily have been selective for cocaine and ethanol (Dess et al. 1998), and it is not necessarily governed by common underlying neurochemical mechanisms involved in cocaine, ethanol and saccharin intake. The lack of a phenotype effect in the cocaine males may have been due to a floor effect, as phenotype scores were quite low in both groups. The absence of a phenotype effect in the heroin groups may have been occluded by a ceiling effect resulting from a dose of heroin that was too high. However, the heroin dose was chosen because it was sensitive enough to reveal sex differences in acquisition of heroin self-administration but not in the subsequent maintenance phase (Lynch and Carroll 1999). Similarly, the present pheno-

type effect found in acquisition was not measurable during the maintenance (PR) phase, and this may have been due to the slight food restriction that was necessary to generate PR performance. Others have shown that food restriction reduced phenotype differences by making different strains of mice more sensitive to the rewarding effects of amphetamine (Cabib et al. 2000). Finally, the sex differences in the heroin rats' rate of acquisition and day 5 (Fig. 1) had disappeared by the last 5 days of the acquisition period (Table 2). In general, the present results and other work indicate that factors such as phenotype, activity level, and sex that predict vulnerability to drug abuse are relatively fragile, as they occur during brief intervals and are often detectable only at low self-administration doses and under conditions in which behavior is in transition such as acquisition (Lynch and Carroll 1999) and reinstatement (Lynch and Carroll 2000). In the present study, the differences between phenotypes were subtle, and their detection required multifaceted behavioral assays. The differences between cocaine and heroin with respect to detecting phenotype versus sex differences occur only at a limited (e.g. threshold) dose range.

The saccharin preference phenotype found with IV cocaine in this experiment and with oral ethanol intake (Dess et al. 1998) is consistent with data from several laboratories using selection for sweet intake in outbred rats (Gosnell and Krahn 1992; Bell et al. 1994; Gahtan et al. 1996; De Sousa et al. 2000). In contrast, the predictive effect of saccharin intake for IV cocaine self-administration (versus heroin) was not found by Gahtan et al. (1996) and Gosnell and coworkers (1998), yet in the same rats there was a relationship between high saccharin intake and ethanol self-administration (Gahtan et al. 1996). A similar experiment conducted with morphine, produced a consistent relationship between saccharin intake and morphine self-administration (Gosnell et al. 1995). Commonality of results might be expected between saccharin and opioids, due to their similar effects on endogenous opioids and opioid receptors, compared with cocaine and saccharin. However, there is evidence for dopaminergic effects of saccharin and other sweeteners (Pothos et al. 1995; Sills and Crawley 1996; Sills et al. 1998; Carr and Kim 2000; Carr and Kutchukhidze 2000) as well as opioid effects.

The present experiment also explored the effect of sex differences within the Occidental HiS, LoS selectively bred strains. The finding that females acquired both cocaine and heroin self-administration more rapidly than males and consumed more drug than males was more robust than the phenotype effect. For example, Table 1 indicates that the LoS females and HiS males have similar, mid-range saccharin phenotype scores, yet the analysis of break point and cocaine infusions under the PR schedule indicate enhanced drug-maintained behavior in females compared with males. The elevated acquisition rates for females compared with males was consistent with several previous reports with cocaine and heroin using similar procedures (Lynch and Carroll 1999; Carroll et al. 2001) as well as under different acquisition and maintenance conditions for caffeine (Heppner et al. 1985), cocaine (Morse et al. 1993), ethanol (Lancaster and Spiegel 1992), fentanyl (Klein et al. 1997), morphine (Alexander et al. 1978), and nicotine (Donny et al. 2000). Previous research with the Occidental rats had also indicated sex differences in ethanol self-administration (Dess et al. 1998). In general, female rats are more active than males, especially during phases of the estrous cycle when estrogen levels are high (Haney et al. 1994; Eckel et al. 2000), and this also applies to drug-induced increases in activity (Becker and Beer 1986; Camp et al. 1986).

Recent data from outbred Wistar rats acquiring cocaine (Lynch et al. 2000 and unpublished data) and heroin (Roth et al. 2002) self-administration, suggest that gonadal hormone (e.g. estrogen) levels may be responsible for these elevated levels of drug intake. There are parallels of this effect in female human subjects that report more positive subjective effects of *d*-amphetamine (Justice and de Wit 1999) and cocaine (Evans et al. 2002) during the follicular phase of the menstrual cycle when estrogen levels are high. In the present experiment HiS female rats also consumed more saccharin, and female rats had higher saccharin phenotype scores than males as has been reported previously (Dess and Minor 1996; Thiele et al. 1997; Dess 2000). HiS females also consumed more of a sucrose, saccharin-glucose, and a saccharin-polycose solution than HiS males (Dess and Minor 1996). Estrogen interacts with the mesolimbic dopamine system (Becker 1990; Thompson and Moss 1994), which is postulated to mediate the reinforcing effects of many drugs of abuse (Di Chiara and Imperato 1988). Female rats also have higher levels of corticosterone (Haney et al. 1994). At the neurochemical level, secretion of glucocorticoids and their mediation of dopaminergic responses to drug self-administration may be at the basis of the interactions among several vulnerability factors such as sex, sweet preference, activity, emotionality, stress and elevated responses to drugs of abuse (Haney et al. 1994; Rougé-Pont et al. 1995; Piazza and Le Moal 1996, 1998; Piazza et al. 2000).

Selective breeding is a useful tool for identifying characteristics that correlate with vulnerability (or resistance) to drug abuse. For example, lines of rats that have been selectively bred for high ethanol consumption consume more saccharin than those bred for low ethanol consumption (Sinclair et al. 1992; Overstreet et al. 1993). In a multiline factor analytic study, saccharin consumption loaded on an ethanol factor (Overstreet et al. 1997). Thus, there is the reciprocal condition in which high levels of ethanol intake predict an avidity for saccharin. Other studies of the Occidental, HiS LoS rats indicated that generally the HiS rats consumed more sweet, salty and starchy solutions than LoS rats, and LoS rats were more sensitive to the aversive effects of a quinine-adulterated sucrose solution (De Francisco and Dess 1998; Dess 2000). HiS rats' avidity for sweet solutions and drugs (cocaine, ethanol) parallels results from

the alcohol-accepting (AA) (Eriksson 1968) and alcohol-preferring (P) (Li et al. 1987) lines of rats selectively bred for higher ethanol consumption (compared to their ANA and NP counterparts, respectively).

Other important correlates of the drug and saccharin intake selection phenotype have been noted. For example, the ethanol preferring phenotype is related to differences in emotionality (e.g. open field defecation, vocalization) and pain sensitivity (Badistov et al. 1995; Kampov-Polevoy et al. 1995b; Overstreet et al. 1997). Factors that control ethanol and cocaine-maintained behavior in rats also control excessive running (Werme et al. 1999, 2000). Similarly, rats selected on the saccharin preference phenotype differed in open field defecation and stress-induced anorexia (Dess and Minor 1996; Dess et al. 2000), acoustic startle, and stress-induced analgesia (Dess et al. 2000). The reverse condition has also been reported; rats selected on the basis of open field defecation differ in their ethanol and saccharin consumption (Adams et al. 1991; Overstreet et al. 1993). Thus, there is a confluence of several factors that affect drug self-administration, such as sex, sweet intake, activity level, stress and emotionality, and they may have a common genetic and neurological basis. A cluster of factors may be more detectable than separate factors for identifying individuals at risk, and they may be more useful in prevention efforts. However, all of these factors may be manifestations of the same underlying neurobiological disturbance or an elevated response to positive environmental stimuli. Thus, it is essential to extend these findings and pursue causal relationships to specify the mechanisms whereby these factors can lead to drug abuse in some individuals but not in others.

In summary, the present results indicate that female rats selectively bred for high saccharin intake acquired IV cocaine self-administration more rapidly, and a greater percentage of the group met the acquisition criterion compared to rats bred for low saccharin intake. As in previous studies with outbred rats, there were sex differences in rats selectively bred for saccharin intake, such that female rats showed faster rates of acquisition and greater maintenance levels (PR) of cocaine self-administration than males. In the heroin groups there was more rapid acquisition in females compared with males but no significant saccharin phenotype differences. Vulnerability factors such as saccharin phenotype and sex are fragile, but these effects are consistent, and they are best revealed at low drug doses and under transition states of drug addiction such as acquisition. It is nevertheless important to recognize these triggering factors as critical to the onset and continuance of drug abuse.

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