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Rats Bred for Differences in Preference to Cocaine: Other Behavioral Measurements

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SCHECHTER, M. D. *Rats bred for differences in preference to cocaine: Other behavioral measurements.* PHARMACOL BIOCHEM BEHAV 43(4) 1015–1021, 1992.—Cocaine has repeatedly been shown to produce conditioned place preference (CPP) in the rat. The present study employed the heterogenous N/Nih rat stock to produce a selectively bred rat line determined by individual place preference to a conditioning dose of 2.5 mg/kg cocaine. As each of three generations of rats were exposed to the CPP task, cocaine-preferring (CP) males were mated with CP females whereas cocaine-nonpreferring (CNP) male rats were paired with their female counterparts. Rats in litters of the third generation of these selectively bred rats were used in two collateral studies: one involving the discriminative stimulus properties of cocaine and the other to investigate the ability of cocaine to stimulate activity. Results indicate that the continued breeding of CP animals has resulted in rats that prefer cocaine, whereas the breeding of CNP rats is defining a line of rats that actually find cocaine aversive. In testing the discriminative stimulus performance of five male CP and five male CNP rats, the learning rates and dose-response relationship to cocaine were not significantly different between these two groups. In contrast, administration of 5.0 and 7.5 mg/kg cocaine to male and female CP and CNP rats indicated that, although all groups were stimulated by cocaine when compared to vehicle administration, male CNP rats showed a significantly decreased reaction to these two doses of cocaine. The possibility that conditioned place preference and locomotor stimulation are subserved by the same neural substrates, that is, most probably the dopaminergic systems in the nucleus accumbens of the brain, is discussed.

Cocaine Selective breeding Conditioned place preference Stimulus properties of drugs
Locomotor activity Rats

THE correlation between the rewarding quality resulting from the first experience with a drug and the eventual habit/addiction produced by that drug has been studied in human abusers. The results indicate that those drugs that are not well liked on the first occasion of use (e.g., major tranquilizers, cigarettes, and glue) results in a decrease in subsequent habit formation, whereas higher positive reinforcement scores found with the initial exposure to the drug, for example, after heroin and cocaine, correlated positively with continued drug use that eventually resulted in abuse (2). An animal model that can be employed to determine preference to initial exposure to a drug is the conditioned place preference (CPP) test. This task pairs low doses of a drug with specific environmental cues/stimuli and subsequently evaluates the rewarding effects of that drug while the animal is in a nondrugged state. The effects of pairing a reinforcing drug with a particular environment influences an animal's behavior so that it will spend more time in that place in which it had the positive experience. This observation is compatible with theories that stress the addiction potential of drugs and appears to be particularly well suited for studying the neuropharmacology of drugs as reward. Cocaine has repeatedly been shown to produce CPP in the rat (1,3,4,8–11,13,16).

Based upon a predisposition for alcoholism that seems to be under genetic (inheritable) influences in humans, there have been manipulations of the gene pool by selectively breeding to develop lines of rats with differential effects after ethanol administration. A large-scale study has been undertaken to determine ethanol-related traits in a heterogeneous rat stock (N/Nih) (15). This N/Nih strain, comprised of rats initially chosen from available outbred strains to reconstitute a new outbred stock, has been successfully employed to establish new lines of rats bred for their differential sensitivity to ethanol-induced sleep time (15) and for ethanol consumption in an ethanol–water choice situation (6). In contrast, as of this writing there has been no published report of the attempt to

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produce a selectively bred rat line using a nonethanol drug of abuse with the N/Nih or other strains.

The purpose of the present study was to determine the variability of preference to cocaine as assessed by the CPP test in a (heterogeneous) group of N/Nih rats. Preliminary evidence indicated that interindividual differences exist as to the ability of drugs to produce a CPP, that is, some subjects showed a decided preference for the drug-paired environment whereas other subjects did not. Once differences in cocaine preference were determined, the aim was to breed the cocaine-preferring (CP) male rats with CP female rats and to breed cocaine-nonpreferring (CNP) male rats with their female counterparts. As members of each generation were impregnated, gestated, born, and matured, they were tested as to their preference to cocaine at approximately 50 days of age. This allowed continuing generations, starting with the original generation (G_0) and, at this writing, continuing on to the third generation (G_3), with selection based upon high or low cocaine preference in the CPP task. In addition, naive siblings of CNP and CP rats that were not to be used in the breeding program were employed to determine the possible differential effectiveness of cocaine in other behaviors, that is, cocaine-stimulated locomotor activity and cocaine-induced discriminative learning.

METHOD

Subjects

Twenty-four male and 24 female N/Nih rats were delivered to this site at 28 days of age from the Small Animals Section of the National Center for Research Resources of the National Institutes of Health. Rats were isolated for 1 week and then placed into individual wire hanging cages and allowed free access to food and water in a vivarium facility with an ambient temperature of 20–22°C; animals were maintained on a 12 L : 12 D cycle with lights on at 0600 h. Behavioral measurements were conducted in a room separate from the animal colony.

CPP Apparatus and Procedure

Place conditioning/testing was conducted in one of four modular test component units (Model 85000, Lafayette Instrument Co., Lafayette, IN). The three-chambered stainless steel apparatus consisted of a center section from which subjects were allowed access into two end sections. A constraint wall (Model 85009) served to restrict the subject's egress from the right or left side of the apparatus during conditioning sessions.

The right and left end sections (20.5 × 30.5 × 20 cm), originally identical, were altered in three sensory modalities to produce discriminable cues: The "dark" side of each unit was illuminated by a 6-W, 30-V, red light bulb and had a smooth, black Plexiglas floor; the "light" side was illuminated by a 6-W, 30-V, white light bulb and had a stainless steel grid floor under which pine wood shavings were placed in the drop pan. Location throughout the chamber was detected by weight-pivot sensors connected to a computer that automatically recorded the time (in seconds) spent in each section of the apparatus.

Subjects underwent three treatment phases. All subjects were first given 2 days of (30 min) habituation to the conditioning room and 15 min of free access to all three areas of the CPP apparatus. On the third day, the 15 min of free access served to establish a "preconditioning baseline" of place preference for each individual rat. The side in which the rat spent less time (in seconds) was considered its nonpreferred side for the remainder of the study. The second phase, "drug conditioning," was then initiated and conducted daily for 30 min over an 8-day period. On alternate days, animals were confined to their nonpreferred side for 30 min after IP administration of 2.5 mg/kg cocaine. On the other days, animals were administered IP an equal volume (1 ml/kg) of saline and confined to their preferred side for the same duration of time. Twenty-four hours following the last (eighth) day of conditioning, each animal was allowed free access, as on the baseline day, for 15 min to determine place preference in a nondrugged state.

The shift in preference, that is, the difference between the number of seconds spent in the nonpreferred side postconditioning with cocaine *minus* the number of seconds spent in this side during baseline (prior to conditioning with cocaine) was the measurement used to determine male and female CP and CNP rats. A positive number would indicate that more time was spent in the nonpreferred side after cocaine conditioning than before cocaine conditioning (a CPP), whereas a negative number would indicate more time spent in the nonpreferred side before cocaine conditioning than after conditioning (a conditioned place aversion).

Selective Breeding

By using the established heterogeneous stock of N/Nih rats, the genetic response pool, as well as the possibility of later comparisons between laboratories, was promoted. The initial breeding stock of 24 male and 24 female rats, designated G_0, included no siblings and at the completion of the first CPP test the 10 males and 10 female rats that showed the greatest shift in preference were paired and housed in breeding units. Similarly, 10 male and 10 female rats with the least preference shift (indeed, those that indicated a conditioned place aversion to cocaine were identified) were paired and caged in 10 breeding units. Pairing in this case matched the least-preferring male with the least-preferring female and so forth. Females were then removed to plastic cages to await delivery and, once born, pups were allowed to nurse for 3 weeks before weaning. At weaning, pups of each litter were randomly culled to a maximum of four males and four females and the sexes allowed to mature separately for another 48 days. Thus, the total number of animals for both lines of the first generation (G_1) were 160 rats during maturation.

At the time that the G_1 generation started preference testing, litters were again culled to three males and three females by random selection. The goal was to start with 10 breeding pairs (and, thus, 10 litters for each line) to allow for losses during breeding and rearing stages. The selection of 16 litters (8 per line) at that time was based upon the prior ranking of the parents' sensitivity to preference shifts with cocaine in each line. Thus, litters of the eight highest ranked of the surviving high-preference pairs were selected for the CP line and litters of the eight lowest ranked of the surviving low-preference pairs were selected for the CNP line.

All 96 animals (3 males and 3 females from 8 litters for each of 2 lines) of the G_1 generation underwent preference testing. Males and females with the highest and lowest preference to cocaine were selected from each litter as breeders for the next cycle. The method for pairing for breeding purposes for the G_1 and G_2 generations was after the procedure described in detail by Poiley (12).

Collateral Testing: Activity

As the genetically specified lines of rats developed from G_0 through G_2, based upon their differences in preference to

cocaine, the involvement of other behaviors, that is, associated processes, was tested. Thus, collateral (correlative) tests of the effects of cocaine on other behaviors were conducted upon siblings of rats in the breeding stock. Five of each of the male CP and CNP and female CP and CNP rats were tested, at G_2, for their individual reactivity (locomotor response) in an apparatus built to indicate locomotor activity. Activity was measured by the interruption of one of four photosensor light sources placed in the wall of a Plexiglas cage measuring 45.5 × 35.5 × 20.5 cm. The sensors were orientated 5.5 cm above the floor and 9.5 cm apart along the wall of the longer side. Each photocell interruption constituted one activity count. Activity counts were recorded simultaneously from eight cages, by a computer, at 5-min intervals throughout a 30-min test session. All activity testing was conducted under light conditions and commenced immediately after IP administration of either saline or 2.5, 5.0, or 7.5 mg/kg cocaine. Activity measurements after saline were conducted on the Tuesdays of each of 3 weeks and the activity after cocaine, in incrementing doses, was conducted on the following day, that is, on Wednesday.

Drug Discrimination

This behavioral paradigm allows rats to be trained to discriminate between cocaine and its (saline) vehicle. The procedure consists of training rats to discriminate a drug state from a nondrug state so that food-deprived rats learn to press one of two identical levers in an operant chamber in the presence of the drug state for positive reinforcement, that is, a 45-mg food pellet (P. J. Noyes Co., Lancaster, NH). In the nondrug state, presses on the other lever produced this reinforcement. Thus, each of the two stimuli (cocaine state and nondrug or saline state) is associated with responding on a particular lever. Actual training took place in 12 standard rodent operant chambers where each chamber had two levers that were 7 cm apart and 7 cm above a grid floor. A food magazine was positioned between these two levers and a single food pellet was delivered into this magazine upon completion of the correct response. Each test chamber was housed in a sound-attenuated outer shell equipped with a 9-W light and an exhaust fan. Solid-state programming equipment (LVB Corp, Lehigh Valley, PA) was located in an adjacent room and used to control the reinforcement schedule, food delivery, and data collection.

In the first phase of discriminative training, rats were trained to press one lever 15 min following IP administration of 1 ml/kg of the (saline) vehicle. Initially, a fixed ratio (FR) 1 reinforcement schedule was used but this ratio was gradually increased over the course of 6 days until an FR 10 was obtained. This procedure was then repeated but the opposite lever was reinforced following injection of the cocaine training dose of 10 mg/kg, administered IP, 15 min before animals were placed into the experimental chamber. The FR 1 schedule on the second lever was gradually incremented over a 4-day period to an FR 10. In the second phase of training, an FR 10 schedule was always used. A pseudorandom injection schedule was employed—V,D,D,V,V;D,V,V,D,D, where V = vehicle, D = drug, that is, 10 mg/kg cocaine—so that animals received five cocaine injections and five vehicle injections over a 2-week period. For each rat, responses on any given day were considered correct if the first lever to receive 10 presses first was the appropriate lever, that is, the cocaine lever after cocaine administration or the vehicle lever after vehicle administration.

An animal was considered trained when the criterion of 8 correct first lever selections out of 10 consecutive sessions was attained. This is known as sessions-to-criterion (STC) and is numerically represented by the first of the 10 consecutive sessions in which 8 correct responses were made according to the substance administered. Once this discriminative criterion was reached by all animals, the cocaine-saline training regimen was limited to every other day to maintain the discrimination criterion. Between these cocaine and vehicle maintenance days, rats were tested with varying doses of cocaine so that each dose was tested twice, once following a cocaine maintenance day and once following a vehicle maintenance day. This counterbalancing was used to control for any possible residual influences from the previous maintenance day. Fifteen minutes following cocaine administration, rats were placed into the operant chamber and immediately removed, without receiving reinforcement, following the 10th response on either lever. Animals were not reinforced on test days to preclude any possible training with a dose of cocaine different from that used in training/maintenance.

Measurements and Statistics

The critical measure for the CPP test was the actual time (in seconds) that rats spent in their nonpreferred side of the apparatus during CPP testing. Only the nonpreferred side was paired with cocaine so as to maximize any shift caused by the rewarding effects of cocaine.

The number of training sessions required to achieve discriminative stimulus control (criterion performance) is expressed as STC measurement. The data collected in the drug discrimination sessions is expressed as both quantal and quantitative measurements. Each measurement provides an indication of lever preference prior to any reinforcement. The quantal measurement is the percentage of rats selecting the drug lever as their selected lever, that is, the first lever pressed 10 times. The quantitative measurement is the number of responses on the drug lever divided by the total number of responses on both the drug and the vehicle lever at the time that the 10 responses had been accumulated on either lever. This fraction is expressed as a percentage. Unlike the (all or none) quantal measurement, the quantitative measurement accounts for responses on both the selected and unselected levers and, thus, provides a measure of the magnitude as well as the direction of lever preference. In addition, parametric statistics may be performed on the quantitative data between groups. The advantages of using both types of measurements are fully discussed by Stolerman and D'Mello (17). Quantal data were compared by a computer-generated formulation of Litchfield-Wilcoxon analysis (19) that yielded ED_{50} values and confidence limits for cocaine dose-response curves.

RESULTS

Breeding for Differences in Preference

The results of three generations exposed to the CPP test, and selected for cocaine preference and nonpreference, appear in Table 1. The 10 female CP rats of the first generation (G_0) spent an average of 282.9 s more in the nonpreferred side after four 2.5-mg/kg cocaine conditioning trials in that side than they did during baseline, whereas the shift in the 10 G_0 male CP rats was even greater (342.7 s). In the 10 female rats with the least amount of shift in this first generation, the difference in time spent after cocaine conditioning was 37.2 s and in male CNP the shift was 70.2 s. Subsequently, the 10 female CP rats were bred with the 10 male CP rats, whereas

TABLE 1
SHIFT IN PREFERENCE: THREE GENERATIONS OF N/Nih RATS

	Mean Seconds (±SD) Spent on NP Side Post Cocaine Conditioning Minus Seconds Spent During Baseline Test			
	Female		Male	
	CP	CNP	CP	CNP
G_0	282.9	37.2	342.7	70.2
	(99.7)	(73.2)	(90.7)	(82.9)
G_1	411.4	−8.4	445.3	58.0
	(108.0)	(171.1)	(181.6)	(154.3)
G_2	309.5	−15.0	317.5	−60.6
	(121.2)	(96.7)	(168.6)	(58.3)

the 10 female CNP rats were mated with the 10 male CNP rats.

Their offspring constitute G_1, and these animals were exposed to the CPP test and the shifts in cocaine preference in the nonpreferred side were once again determined. When all male rats bred from CP parents are considered, the mean shift was 148.8 s (with a range of 564 to −172 s) whereas the mean shift of CNP-parented male rats was 66.4 (range: 331 to −126) s. Likewise, female offsprings bred from selected CP parents produced a mean shift of 159.3 s in contrast to all CNP females' mean shift of 106.8 s. Because of the large deviations between the maximum and minimum shifts observed when all rats of each generation were considered, only the mean shifts of those rats selected for breeding are given in Table 1. Rats from each of the female CP and CNP, as well as the male CP and CNP, were selected to be bred for G_2. The mean shifts (±SD) for this generation indicated that, as before, the shift in preference in female CP animals (411.4 s) was significantly ($p < 0.01$) greater than the shift seen in CNP rats (−8.4 s), as was the shift in preference in male CP (445.3 s) vs. male CNP rats (58.0 s). In fact, both female and male CP rats showed a greater shift than was seen in animals selected in G_0, whereas female and male CNP animals of G_1 showed a diminished preference shift. This would indicate a tendency toward less preference was occurring in CNP rats. Further, the mean shift in preference for the nonpreferred side as shown in female CNP rats of G_1 was actually negative (−8.4 s), indicating these rats spent more time in the nonpreferred side during baseline preconditioning than they did post-cocaine conditioning. This would suggest that, on average, these animals are beginning to find cocaine less than preferable.

Table 1 also shows the latest generation, as of this writing, that is, G_2 of CP and CNP male and female rats. Although the positive mean shift in preference in both female and male CP rats has decreased somewhat from that seen in G_1, the mean shift in preference in both female and male CNP animals continues to decline with both groups showing negative values. As siblings of these rats were used in the activity and drug discrimination experiments (below), it is interesting to look at some of the typical litters produced in G_2 in that many CP rats, both male and female, come from the same parentage. Thus, for example, CP rats 2 and 3 are male offsprings and rat 4 is the female offspring from parents 26 and 77, who were CP rats in G_1. In addition, CP rats 9 and 11 are two "brothers," with two "sisters" (7 and 8), from the same parents (86 and 92), which were CP rats of G_1. This same apparent effect is occurring in CNP rats where, for example, there were two males and one female from the same parents and one brother and two sisters from the same CNP parents. In all cases, there is no overlap between the two groups, that is, parents found to be CP in G_1 have offsprings that were CP in G_2 and parents that were CNP in G_1 had offsprings that were CNP in G_2. Again, only one of these sisters or brothers was used for breeding purposes with the other sibling(s) employed in the collateral, that is, either the activity or discrimination, study.

Drug Discrimination

Employing five male CP and five male CNP rats of G_2 in a drug discrimination paradigm using 10 mg/kg cocaine as the training dose yielded results shown in Table 2. The mean STC for CP and CNP animals was 5.6 and 6.6 sessions, respectively, which was nonsignificantly different. During the maintenance cocaine sessions, interspersed during dose–response drug discrimination trials, four of the five CP rats chose the cocaine-correct lever during the first trial whereas all of them chose this lever during the second trial. This is indicated by (9/10) 90% quantal responding at 10 mg/kg cocaine. Similarly, CNP rats had errorless discrimination after the training dose. Decreasing doses of cocaine in general produced decreasing discrimination and the ED_{50} value for CP rats (4.39 mg/kg) was not significantly different (19) from the ED_{50} value (2.49 mg/kg) generated from dose–response data in CNP animals.

As an independent control, 10 experimentally naive rats of Sprague-Dawley descent were trained to discriminate 10 mg/kg cocaine at exactly the same time and in the same apparatus using the same procedure. Their STC was 5.6 (±3.2; range 2–12) sessions and their quantal discrimination measurement after 10, 5, 2.5, and 0 mg/kg cocaine was 95, 55, 50, and 10%, yielding an ED_{50} value of 3.04 mg/kg. The STC and ED_{50} value was not significantly different from that determined in either CP or CNP rats.

Locomotor Activity

Administration of saline on the Wednesday of each of 3 consecutive weeks, followed by 30-min exposure to the activity chambers, produced activity counts that were not significantly different between weeks and were not significantly different between groups (data not shown). Administration of 2.5 mg/kg cocaine to female CP and CNP rats, as well as male CP and CNP rats, produced no significant difference between

TABLE 2

LEARNING RATE AND DOSE-RESPONSE EFFECT OF COCAINE DISCRIMINATION IN MALE CP AND CNP RATS

	CP (n = 5)		CNP (n = 5)	
Dose Cocaine	Quantal	Quantitative (SD)	Quantal	Quantitative (SD)
10.0	90.0	75.9 (4.9)	100.0	90.1 (3.5)
5.0	40.0	50.3 (4.7)	50.0	49.5 (9.8)
2.5	30.0	40.9 (32.4)	60.0	58.1 (9.1)
0.0 (veh)	20.0	30.5 (7.7)	0.0	12.0 (14.1)
ED_{50}	4.39 mg/kg		2.49 mg/kg	
(95% CL)	(2.74–7.05)		(1.06–5.85)	
STC (SD)	5.6 (±2.7)		6.6 (±2.6)	
Range	2–9 sessions		3–10 sessions	

groups as shown in Fig. 1. In contrast, 5.0 mg/kg produced elevations in activity after cocaine in all but male CNP rats, a group that showed a significantly reduced stimulant effect after 5.0 mg/kg cocaine. Thus, in male CP rats the mean activity (±SD) counts determined after cocaine *minus* those counts after saline was 171.8 (68.8), whereas in male CNP rats given the same dose of cocaine this mean difference was 13.6 (39.2) counts. These values were significantly different (t = 4.468). Likewise, testing a dose of 7.5 mg/kg in all four groups of rats indicated that the stimulatory effect of this dose of cocaine was reduced in male CNP animals in that these animals showed a difference between cocaine and saline of 194.0 counts, in contrast to male CP rats, which showed a difference of 347.2 counts, significant at $p < 0.01$ (t = 4.041).

DISCUSSION

In an attempt to determine differences in the initial preference/aversion of rats to a low dose of (2.5 mg/kg) cocaine, the CPP task was employed using N/Nih rats. Although selective breeding has only occurred in two generation, the results (which may be viewed as preliminary) suggest that interindividual heterogeneity to cocaine preference exists, with the ma-

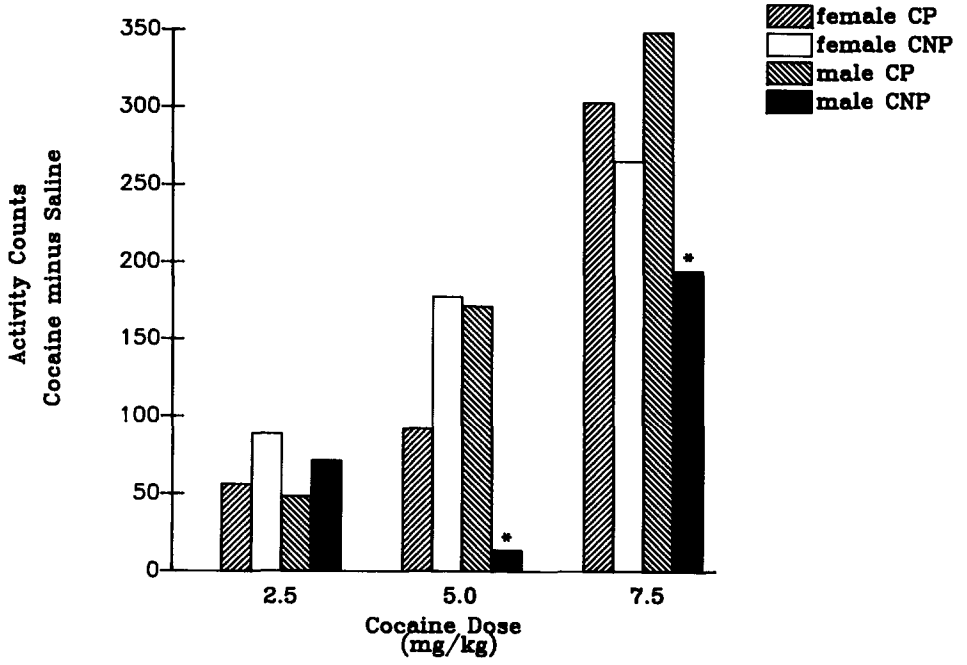

FIG. 1. Stimulation of activity after 2.5, 5.0, and 7.5 mg/kg cocaine IP in female cocaine-preferring (CP) and nonpreferring (CNP), as well as male CP and CNP rats (five per group) of the third generation of selectively bred rats. Ordinate: number of photobeam crosses after cocaine minus number of photobeam crosses after saline IP on the preceding day; abscissa: dose of IP cocaine in mg/kg. *Significant ($p < 0.01$) difference from male CP at same dose.

jority of rats preferring this drug [as repeatedly seen in the literature; see (3)]. Interestingly, a small number of G_0 rats exhibited a reduced preference and the number of rats that exhibited a conditioned place aversion to cocaine (defined as a decreased amount of time spent in the cocaine-paired environment) increased in CNP rats from G_0 to G_2. It appears that what may actually be occurring in continued selective breeding is that animals are being bred away from the typical behavioral response, that is, preference for cocaine. Thus, CNP rats developed by continued breeding/generations may find cocaine to be even less rewarding/reinforcing. This separation from the norm may have existed (although not known with certainty) when rats were being bred for preference and nonpreference to ethanol drinking in that the earliest "separations" may have been observed in animals starting to prefer alcohol as indicated by drinking larger amounts than normally seen. Thus preferring rats were being bred away from the norm, that is, rats were being bred that did not conform to the general finding regarding the aversive gustatory effects of ethanol. Continuing breeding of rats finding cocaine less preferable may allow future study of the inherited susceptibility to the abuse potential of cocaine.

Five male littermates of each of the CP and CNP rats that went on to be used for breeding purposes were used in the drug discrimination paradigm. Results indicate that there is no significant differences in either their learning rates or sensitivity to decreasing doses of the drug as indicated by their ED_{50} values. Thus, it appears that the drug discrimination paradigm may not only require a higher (10 mg/kg) dose of cocaine than used in the CPP task but also may be of a higher order of learning as to overpower any differences that may be apparent by selective breeding. In fact, recent evidence from this laboratory, using rats selectively bred for the differential behavioral effects of ethanol over many generations, has shown rats to respond similarly when trained to discriminate ethanol. Thus, HAS/LAS rats, selectively bred for alcohol sleep time, showed the same effect to the discriminative stimulus properties of ethanol (14) and HAD/LAD rats, selectively bred for alcohol drinking preference, responded differently to the stimulating effects of ethanol but not to its discriminative effects (5).

In contrast to similar drug discrimination effects in CP and CNP rats, there were differences in the ability of cocaine to produce stimulation of locomotor activity in that the stimulatory effects of both 5.0 and 7.5 mg/kg cocaine produced less activation in male CNP animals than it did in male CP animals. The reason that a similar significant increase in the activity of female CP vs. CNP rats did not occur is, at present, unknown. This observation in male rats is of interest because the positive reinforcing/rewarding properties of cocaine may be derived from the hyperactivity elicited by cocaine. This hypothesis has been posited (18) in that the level of activity experienced by an animal within the specific environment may alter its subjective experience of that environment. Thus, rats that receive cocaine within a specific environment (their nonpreferred side) may experience that environment in a context of higher levels of exploration and familiarization. This was observed in that male CP animals showed both increased locomotor activity and cocaine preference, whereas male CNP animals showed both (by definition) less preference and less stimulation. In this regard, the neural substrates that effect CPP as they are produced by cocaine may involve the dopaminergic neurons in the nucleus accumbens, a brain site also shown to mediate the locomotor activating properties of cocaine (9). In contrast, other investigators (7) have suggested that locomotion and place preference are behaviors that are subserved by different "neuronal populations, or . . . by different levels of activation in the same set of neurons." Just why only male rats that found cocaine less preferable (rewarding) in the CPP test would not be as activated by its administration remains to be determined but, assuredly, these two measurements will be collaterally investigated in continued work with generations selectively bred for cocaine preference.

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