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Locomotor Response to Novelty Does Not Predict Cocaine Place Preference Conditioning in Rats

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GONG, W., D. B. NEILL AND J. B. JUSTICE, JR. *Locomotor response to novelty does not predict cocaine place preference conditioning in rats.* PHARMACOL BIOCHEM BEHAV 53(1) 191–196, 1996.—Previous studies have demonstrated that rats showing a strong locomotor response to a novel environment have a greater locomotor response to psychostimulant drugs and more rapidly acquire intravenous self-administration of amphetamine. In this report, we examined whether these high-responder (HR) rats would develop place-preference conditioning with cocaine more readily than low-responder (LR) rats. Neither group of rats developed conditioned place preference for cocaine, 2.5 mg/kg, intraperitoneally (IP). Both groups of rats developed conditioned place preference for cocaine, 5.0 and 15 mg/kg, IP. However, we could not find any evidence of enhanced conditioning in the HR rats. HR rats did show a greater locomotor response to cocaine, 15 mg/kg, IP, and the locomotor response of HR and LR rats to cocaine correlated with their response to a novel environment. We conclude that using the place-preference procedure, HR and LR rats do not differ in the rewarding effect of cocaine.

Cocaine Conditioned place preference Individual differences Reward Novelty Locomotor activity High responder Low responder

IT HAS BEEN shown that rats with a high locomotor response to a novel environment (HR rats) more readily acquire low-dose amphetamine self-administration than those with a low locomotor response (LR rats) (20). HR rats also exhibit an enhanced locomotor response to low-dose amphetamine (11,13) and cocaine (12,13). Piazza et al. (21) reported a higher DOPAC/dopamine ratio, implying higher dopaminergic activity, in tissue from nucleus accumbens (NACC) of HR rats. Using in vivo microdialysis, HR rats have been shown to have a higher basal level of dopamine in the NACC than LR rats (10). Compared to LR rats, HR rats display a greater increase in extracellular dopamine in NACC in response to amphetamine (1) and cocaine (12), although when expressed as percent baseline, the cocaine-induced increase in the two groups is not significantly different (10).

These data provide some useful information about behavioral differences between HR and LR animals in reaction to psychostimulants and a possible neurochemical mechanism. However, most of the behavioral studies of drug responses in these animals have used locomotion. As mentioned earlier, the original definition of HR and LR rats used the acquisition of responding for intravenous (IV) self-administration (20). In the self-administration procedure, subjects are required to make an operant response to receive a predetermined dose of a drug. Although self-administration is widely used as a measure of the abuse liability of drugs (15), an alteration in motor activity may interfere with or enhance an animal's ability to perform the operant response required to obtain the drug. This confound has limited the interpretation of some self-administration studies (15). In the case of HR and LR rats, it is possible that the locomotor difference between the two groups may contribute to their difference in the acquisition of bar pressing for amphetamine.

Conditioned place preference (CPP) provides another method of assessing the rewarding efficacy of a drug. In this procedure, unconditioned stimuli in a previously neutral environment are paired with a drug. By virtue of Pavlovian conditioning, these stimuli may acquire rewarding properties (9). In drug reward studies employing the CPP paradigm, subjects are exposed to a box typically consisting of two major compartments joined by a short third compartment. The two major compartments differ in floor texture, wall color, or other

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distinctive environmental stimuli. Drug presentation is paired with confinement to one of the major compartments and vehicle presentation with the other major compartment. Later, in the absence of the drug, if the subject spends a greater amount of time in the drug-paired compartment compared with the vehicle-paired compartment, then a CPP is said to have occurred, and the drug is considered to be rewarding. The CPP paradigm has been used widely to demonstrate the rewarding properties of psychomotor stimulants and other addictive drugs (2,9,24). Most drugs that produce a significant CPP are also self-administered IV (2).

EXPERIMENT 1: PLACE PREFERENCE CONDITIONING WITH LOW DOSES OF COCAINE

For the analysis of drug reward in HR and LR rats, an important aspect of CPP is that behavioral testing takes place when the animal is in a drug-free state; thus, the difficulties associated with drug-induced motor activity are minimized. Another strength of CPP is the minimal number of exposures required for the expression of reinforcement. Usually it takes only two to four drug pairings to establish psychostimulant-induced CPP (2). Piazza et al. (20) reported that four exposures of a moderate dose of amphetamine (1.5 mg/kg) changed LR rats to HR rats in both their locomotor responses to amphetamine and the acquisition of amphetamine self-administration. Horger et al. (14) found that preexposure facilitated acquisition of IV self-administration of cocaine. Therefore, minimizing the number of drug exposures by using the CPP procedure becomes particularly important in studying the difference between HR and LR rats. Finally, CPP is a very sensitive measure of reward. It has been shown that doses of cocaine too low to enhance locomotor activity significantly can reliably produce a significant CPP (25,26). The combination of reduced drug exposure and use of low doses in the CPP procedure permitted us to test the drug reward of HR and LR rats while decreasing the roles of sensitization and locomotion.

Method

Subjects. Male outbred Sprague-Dawley rats (Harlan Sprague-Dawley, Inc., Indianapolis, IN), weighing 290-330 g at the beginning of testing, were used. Animals were housed three to four per cage and maintained on a 12 L : 12 D (lights on 0800 h) with food and water continuously available. Experimentation took place during the light phase of the cycle.

Apparatus. The locomotion test was performed in clear, rectangular Plexiglas boxes (41 × 41 × 31 cm) placed inside Digiscan optical activity monitors (Omnitech, Columbus, OH). The monitors were equipped with eight infrared light beams and associated photocells spaced 4.5 cm apart on two perpendicular sides. A locomotor count required the consecutive breaking of two different beams. A computer totalled locomotor counts in 1-min intervals.

The CPP test was performed in opaque Plexiglas chambers (80 × 25 × 35 cm) divided into three separate compartments. The two main compartments (34 × 25 cm) were separated by a small neutral compartment (11 × 25 cm), which was used as the place of introducing the animal on the pretest and test days. The neutral compartment had sheet aluminum flooring and was separated from the two main compartments by gray walls that had 12 × 16 cm passageways cut in them that could be occluded by removable guillotine doors. One of the main compartments had black walls and a floor of 6.4 mm diam. metal rods spaced 25 mm apart; the other had white walls and a metal mesh floor (6.4 mm spacing of 1-diam.-mm wires).

Procedure. This experiment consisted of two behavioral tests: a locomotor screening test and a CPP test.

Locomotor screening test. First, 48 rats were screened in the locomotion box for 30 min each. Rats whose locomotor readings were in the top third of the 48 were labeled as HR rats. Rats whose locomotor readings were in the bottom third were labeled as LR rats. Half of the animals of each group received 2.5 mg/kg cocaine in the following CPP test; the other half received 5.0 mg/kg cocaine.

CPP test. The CPP test consisted of three phases: preconditioning, conditioning, and postconditioning. During all phases, testing was carried out between 1300 and 1700 h.

In the preconditioning phase (1 day), subjects were placed in the neutral compartment and the guillotine doors were removed to allow access to the entire apparatus for 15 min. The amount of time spent in each compartment was monitored and used to assess unconditioned preferences. The preferred side was defined as the black or white one in which the rat spent the greatest amount of time. The number of entries to each compartment was also recorded. In this and each phase, compartments were cleaned and bedding located below the flooring was changed after each rat.

During the following conditioning phase (4 days), subjects were given an intraperitoneal (IP) injection of either a vehicle solution (1 ml/kg) or cocaine HCl (2.5 or 5.0 mg/kg) on alternate days. These doses of cocaine were among the lowest found to produce a reliable place preference (26); they were chosen because the nature of this study was to examine a possible sensitivity difference to the rewarding properties of cocaine. The rats in each treatment group were counterbalanced according to the side of initial preference and sequence of drug or vehicle treatment. Each subject received two drug and two vehicle pairings. Half of each treatment group received drug injections on the 1st and 3rd day; the remaining subjects received drug injections on the 2nd and 4th days. This type of totally balanced experimental design, in which the mean amount of time spent in the two compartments is equated for the group before drug pairing, has been argued (2) to allow a clearer measure of the rewarding properties of a drug than biased designs in which the drug is paired with the least preferred compartment.

Immediately following the injections, subjects were confined to the appropriate compartment for 30 min with access to the neutral compartment blocked by the guillotine door.

For the postconditioning phase, the day after the last conditioning trial, subjects were tested once for their preference in a drug-free state. Each rat was placed in the neutral compartment with the guillotine doors removed and was allowed free access to the entire apparatus for 15 min. The amount of time spent in each compartment was recorded to assess individual preferences. The number of crossings from one compartment to another was also recorded.

Drug administration. The cocaine hydrochloride used in this study was provided by the National Institute of Drug Abuse. All doses are expressed as the salt. The drug was dissolved in 0.9% saline for IP injection.

Statistical analysis. For each dose group, the time spent on each side was analyzed by a group (HR vs. LR) × compartment (cocaine-paired vs. saline-paired) analysis of variance (ANOVA) with repeated measures on compartment. This analysis, which examined postconditioning data only, was chosen because, with the counterbalanced design, times in the two compartments are equated in the preconditioning test and

analysis of postconditioning data only is typically done (2). The locomotor data from the screening test were subjected to Student's *t*-test. The accepted level of significance was $p < 0.05$ for all statistical tests.

Results

Figure 1 illustrates that HR rats generated approximately twice as many locomotor counts as LR rats in the screening test. Because the groups were defined by activity scores that did not overlap between groups, these differences were necessarily significant (group later receiving 2.5 mg/kg: $t = 6.34$, $df = 14$, $p < 0.001$; group later receiving 5.0 mg/kg: $t = 8.54$, $df = 14$, $p < 0.001$).

Analysis of the preconditioning data showed that after assigning the cocaine- and saline-paired compartments for each rat, time spent in these compartments did not differ in either group that subsequently received 2.5 [$F(1, 14) = 0.034$; NS) or 5.0 mg/kg cocaine [$F(1, 14) = 0.00$; NS). That is, within each group, the rats had no significant side preference.

The abilities of 2.5 and 5.0 mg/kg cocaine to establish a CPP are summarized in Figs. 2 and 3. At 2.5 mg/kg, no significant difference between the time spent in the cocaine-paired side and saline-paired side occurred [$F(1, 14) = 2.57$; NS). At 5.0 mg/kg, a significant overall conditioning effect of cocaine was found [$F(1, 14) = 7.93$; $p < 0.05$]. However, there was no significant group × compartment interaction for the effect of cocaine [$F(1, 14) = 0.39$; NS).

In summary, 2.5 mg/kg did not induce a preference in either HR or LR rats. A dose of 5.0 mg/kg produced a conditioned preference, but HR and LR rats did not differ in the degree of preference.

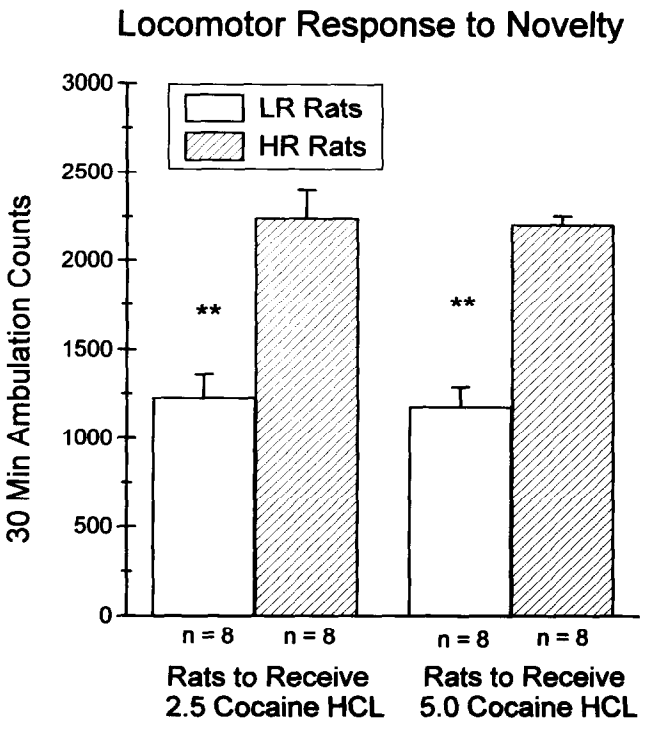

FIG. 1. Mean (±SEM) total locomotor counts after 30 min in a novel testing chamber (screening test). HR (high responder) rats generated significantly more locomotor counts than LR (low responder) rats. $^{**}p < 0.01$, comparing LR and HR rats in each drug group.

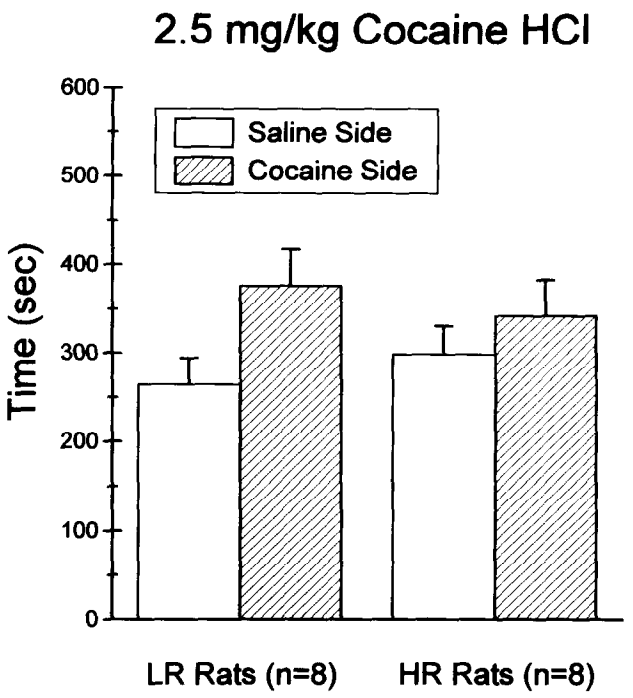

FIG. 2. Place conditioning with 2.5 mg/kg, cocaine IP. Bars represent the mean (±SEM) amount of time spent in the saline- or cocaine-paired compartment on the test day. Neither HR (high responder) nor LR (low responder) rats developed a significant conditioned place preference.

EXPERIMENT 2: PLACE PREFERENCE CONDITIONING AND VERIFICATION OF A HIGH-LOW DIFFERENCE IN THE LOCOMOTOR EFFECT OF 15 mg/kg COCAINE

Experiment 1 did not demonstrate a difference in cocaine reward between HR and LR rats. Consistent with previous reports (7,26), we observed a CPP with 5.0 mg/kg cocaine. Spyraki et al. (26) reported that 2.5 mg/kg cocaine could induce a place preference, but only when the drug was paired with the initially nonpreferred side; we did not find conditioning to either the preferred or the nonpreferred side. Another procedural difference between this study and that of Spyraki et al. is that they paired their rats with cocaine four times but this study paired the rats with cocaine twice. The increased number of pairings increases the strength of a CPP (3,17). However, an increased number of drug pairing also increases drug exposures, which by sensitization may interfere with the measurement of differences in sensitivity to cocaine reward.

In our experience with the rat strain and supplier used in the present experiments, neither 2.5 nor 5.0 mg/kg cocaine induced significant locomotor activity (16). It is possible that the doses employed in Experiment 1 were too low to reveal a CPP difference between HR and LR rats. Even though HR and LR rats were initially reported to be different in acquisition of IV self-administration of low-dose amphetamine (20), this may not necessarily be true for cocaine. The following experiment was therefore conducted to test CPP in our animals with a higher cocaine dose. In addition, we also exam-

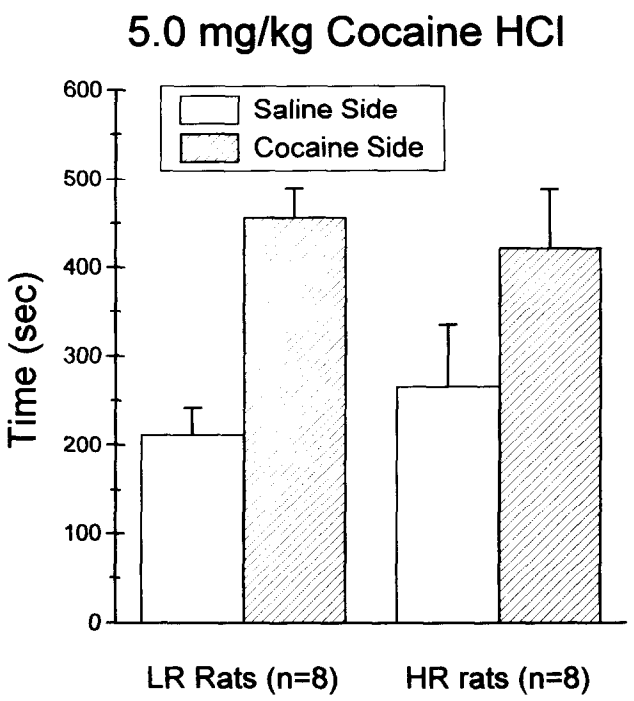

FIG. 3. Place conditioning with 5 mg/kg cocaine, IP. Bars represent the mean (±SEM) amount of time spent in the saline- or cocaine-paired compartment on the test day. Although this dose induced a significant preference for the cocaine-paired compartment in both groups, there was no significant group × compartment interaction.

ined the locomotor response of HR and LR rats to cocaine to verify that the HR rats and LR rats employed in the present study differed in their locomotor response to cocaine as previously reported (12,13). Because we wanted to use a dose known to affect HR and LR rats differentially, we chose 15 mg/kg rather than 10 mg/kg, which would otherwise have been the next dose in the series begun in Experiment 1. The dose of 15 mg/kg has been reported to produce a locomotor response that correlates with the locomotor response to novelty, and to elicit a significantly higher extracellular dopamine level in nucleus accumbens of HR compared to LR rats (10,12).

Method

Subjects. Adult male Sprague-Dawley rats, weighing 290–330 g, were screened using the procedure described in Experiment 1. This resulted in 12 HR and 12 LR rats. Six HR rats and six LR rats were selected randomly and assigned to the CPP study. The remaining six HR and six LR rats were assigned to the locomotor activity study.

Procedure.

CPP conditioning. The CPP procedure was identical to that of Experiment 1, except that a higher dose of cocaine (15 mg/kg) was used.

Locomotor response to cocaine. One day after screening, six HR rats and six LR rats were exposed to the Digiscan chamber 30 min/day for 2 consecutive days. On the 3rd day, the rats were injected IP with 1 ml/kg 0.9% saline 10 min before the 30-min locomotion test. This injection and recording procedure was repeated on day 4 with 15 mg/kg cocaine HCl. On days 5 and 6, saline and cocaine injections were respectively repeated. Thus, as in the CPP study, each animal received two injections of saline and two injections of cocaine; the average of the locomotor scores for the 2 test days for each injection condition was used to assess locomotor responses to saline and cocaine.

Results

The HR rats assigned to the CPP study showed significantly more locomotor activity in response to novelty than the LR rats (t = 4.94, df = 10, $p < 0.001$) as did the HR rats that were assigned to the locomotor activity study (t = 8.67, df = 10, $p < 0.001$).

Analysis of the preconditioning data revealed no overall compartmental preference [$F(1, 10) = 0.64$], difference between HR and LR rats [$F(1, 10) = 0.06$], or interaction between compartment and group [$F(1, 10) = 0.13$].

As shown in Fig. 4, two pairings of 15 mg/kg cocaine with a particular compartment resulted in a significant overall preference for that compartment [$F(1, 10) = 10.47$; $p < 0.01$], but no significant interaction between group and compartment [$F(1, 10) = 0.903$; NS].

Locomotor activity data are summarized in Fig. 5. HR rats showed significantly higher locomotor counts than LR rats during the screening test (t = 8.674, df = 10, $p < 0.001$]. The locomotor response to cocaine was analyzed by ANOVA for repeated measures across the average locomotor counts after saline injection and the average locomotor counts after cocaine injection. Significant group [$F(1, 10) = 6.80$; $p < 0.05$] and treatment [$F(1, 10) = 182.7$; $p < 0.001$] differences

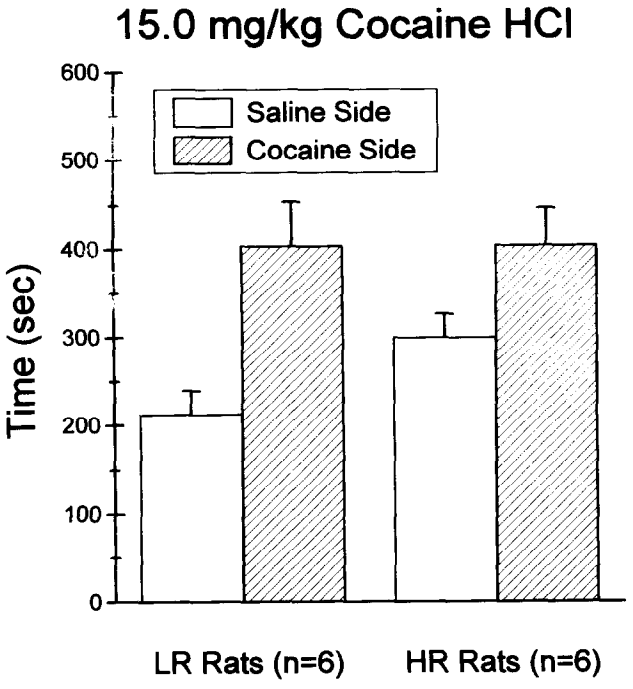

FIG. 4. Place conditioning with 15 mg/kg cocaine, IP. Bars represent the mean (±SEM) amount of time spent in the saline- or drug-paired compartment on the test day. This dose induced a significant preference for the cocaine-paired compartment, but no significant interaction between group and compartment.

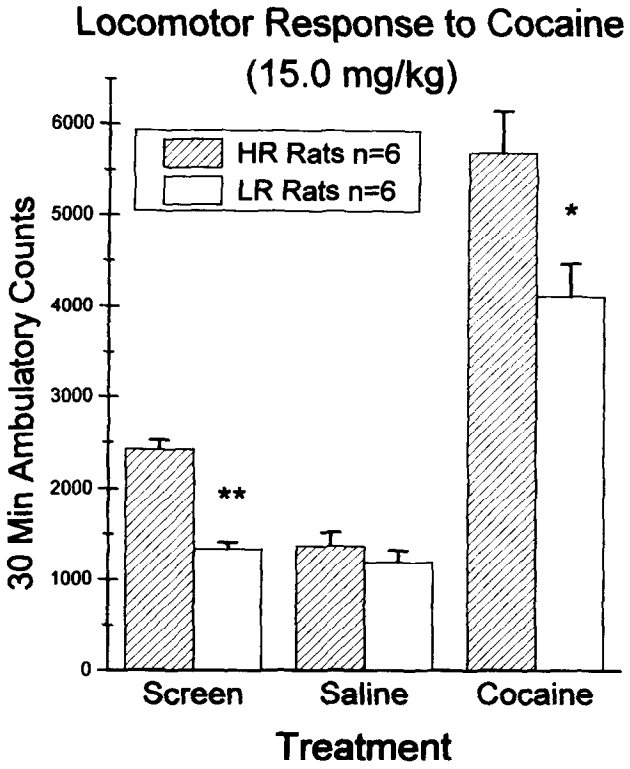

FIG. 5. Locomotor response to 15 mg/kg cocaine, IP. Bars represent the mean (±SEM) locomotor counts in 30-min tests. HR rats showed significantly higher locomotor counts than LR rats during the screening test (**$p < 0.001$). This difference had disappeared by the third exposure to the test chamber, when saline was administered. A significant HR-LR difference reappeared upon administration of cocaine (*$p < 0.01$).

were found. The interaction between group and treatment was also significant [$F(1, 10) = 6.78$; $p < 0.05$]. Subsequent Bonferroni t-tests show that HR and LR rats did not differ in their locomotor response to saline ($t = 2.39$, $df = 10$, NS), but differed in their locomotor response to IP injection of 15 mg/kg cocaine ($t = 21.625$, $df = 10$, $p < 0.05$). A significant correlation between locomotor response to novelty and locomotor response to 15 mg/kg cocaine was also revealed (Pearson correlation coefficient = 0.65; $p < 0.05$).

The numbers of crossings from one compartment to another before and after conditioning were also analyzed by a trial × group two-way ANOVA. No significant difference between groups [$F(1, 10) = 0.007$; NS], between before and after conditioning [$F(1, 10) = 1.299$; NS), or interaction [$F(1, 10) = 0.192$; NS] was observed.

DISCUSSION

The results of this study show that HR rats, which display a greater locomotor response to novelty and cocaine than LR rats, do not show a correspondingly greater CPP with cocaine. These results are in agreement with those of Erb and Parker (3), who did not find an HR-LR difference in CPP with amphetamine. Before considering any possible theoretical significance of this result, methodologic considerations must be addressed.

First, the CPP methods employed in our study may not have been sensitive enough to detect differences between HR and LR rats. The CPP paradigm is generally believed to be a sensitive measure of drug reward (2,26). Cocaine-induced CPP has been demonstrated at doses too low to induce significant locomotor activity change (25,26), even though these studies have paired the cocaine with the initially nonpreferred side (biased design). It can be argued that the counterbalanced design we used may not be as sensitive as a biased design. However, examination of our results did not indicate an HR-LR difference at any dose when conditioning to the nonpreferred side was selectively considered. In addition, using the same procedure employed in this experiment, we (5) demonstrated that rats with septal lesions showed an enhanced place preference to 2.5 mg/kg cocaine. This result suggests that our procedure was sensitive enough to detect a difference in sensitivity to low-dose cocaine reward. Finally, if HR rats are more sensitive to the rewarding effects of cocaine, but this enhanced sensitivity is somehow buried in the counterbalanced design or the dose range we employed, we would expect to see in our data at least some tendency for HR rats to develop a better CPP for cocaine. On the contrary, we consistently observed that the magnitude of CPP tended to be lower in HR rats than LR rats for each dose (Figs. 2–4), even though the tendency was not significant. This nonsignificant tendency for LR rats to develop better CPP was also reported by Erb and Parker (3) for amphetamine.

Second, it might be thought that the difference in drug reward between HR and LR rats is restricted to amphetamine. Even though amphetamine and cocaine share most of their behavioral properties, rats will self-administer amphetamine (8,19) but not cocaine (4) into nucleus accumbens; intra-accumbens injection of amphetamine but not cocaine will produce CPP (7); and some c-fos evidence (6) suggests the two drugs activate different neuronal populations. A recent study (23) found that naloxone blocked the locomotion and attenuated the usual increase in extracellular dopamine in nucleus accumbens induced by amphetamine, but did not block the locomotion and increased dopamine from cocaine. These findings imply that the effect of amphetamine may involve opioid action but the effect of cocaine may not. Taken as a group, these results raise the possibility that even if HR rats do not show an enhanced CPP response to cocaine, they may still show an enhanced CPP response to amphetamine. The evidence against this possibility is the report by Erb and Parker (3) that HR and LR rats do not differ in developing CPP to amphetamine.

After considering this and combining our results using cocaine with those of Erb and Parker (3), who used amphetamine, we conclude that HR and LR rats do not differ in psychostimulant reward as measured by CPP. The majority of the evidence suggesting that HR and LR rats differ in their responses to psychostimulants derives from locomotor studies (11–13). The only study that has revealed a possible difference between HR rats and LR rats in psychostimulant reward measured acquisition of a bar press for IV self-administration (20). Considering the consistent finding that HR rats show an enhanced locomotor response to psychostimulants, it is possible that the enhanced acquisition of IV self-administration reflects an enhanced locomotor response. In the CPP procedure, the reward effect of cocaine was tested in a drug-free state, so any difference in the locomotor response to psychostimulants will have little effect on the expression of reward. As demonstrated in our second experiment, and in agreement with the literature, our HR rats did express more

locomotor activity in response to 15 mg/kg cocaine, but did not show a facilitated CPP.

It can be argued (3) that because HR rats locomote more, they may visit the drug-paired and vehicle-paired compartments more frequently, interfering with their expression of place preference. However, examination of our crossing data did not reveal any difference between HR and LR rats in intercompartmental crossings during pre- or postconditioning tests.

If the facilitated acquisition of IV self-administration of psychostimulants in HR rats is actually an artifact of a greater locomotor response to the drug and not an enhanced reward effect, this implies that the neural mechanisms for psychostimulant reward and locomotion are separable. Wise and Bozarth (27) argued that the neural mechanisms for approach behavior, revealed in part by locomotor activity, are identical to those for reward. Some recent evidence suggests that the reward and locomotion systems are separable. Hemby et al. (7) found locomotion but not CPP from intra-accumbens cocaine. Neurotensin injections in nucleus accumbens have been reported (22) to block the locomotor effect but not IV self-administration of cocaine. Olmstead and Franklin (18) found that lesions of the pedunculopontine nucleus, an output structure of the nucleus accumbens, blocked CPP but not locomotion from amphetamine. If the mechanisms by which psychostimulants induce hyperactivity are separable from those by which they produce CPP, HR rats might show an exaggerated response to these drugs in the locomotor, but not the reward, mechanism.

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