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Locomotor and Rewarding Effects of Amphetamine in Enriched, Social, and Isolate Reared Rats

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BOWLING, S. L. AND M. T. BARDO. *Locomotor and rewarding effects of amphetamine in enriched, social, and isolate reared rats.* PHARMACOL BIOCHEM BEHAV 48(2) 459–464, 1994.—This study examined the influence of environmental enrichment on the behavioral response to amphetamine. Beginning at 21 days of age, rats were raised in one of three different environmental conditions: a) an enriched condition (EC), in which animals were caged in groups and provided with novel objects daily; b) a social condition (SC), in which animals were caged in groups without any novel objects; and c) an isolated condition (IC), in which animals were caged individually without any novel objects. At 53 days of age, animals from each environmental condition were assessed for amphetamine-induced changes in locomotor activity and reward using the conditioned place preference (CPP) paradigm. Results from saline-injected control animals indicated that EC animals exhibited less vertical activity than IC animals when exposed to the CPP apparatus. When challenged with amphetamine (0.5 or 2.0 mg/kg), there were no significant differences between SC and IC animals in either locomotor behavior or CPP. However, EC animals exhibited more horizontal and vertical activity following amphetamine than both the SC and IC animals. Similarly, EC animals exhibited a greater magnitude of amphetamine-induced CPP than both the SC and IC animals.

Amphetamine Environmental enrichment Locomotor activity Conditioned place preference Drug reward Differential rearing

IT is well known that individuals differ in their sensitivity to drugs. Recent research has shown that individual differences in sensitivity to amphetamine in rats may be predicted, at least in part, by their reaction to novel stimulation (21). That is, animals that show a high rate of activity in a novel environment show an enhanced response to the locomotor stimulant and rewarding effects of amphetamine relative to animals that show a low rate of activity in a novel environment.

Although individual differences in response to drugs are under some genetic control (7), evidence also points to an important role for environmental factors. For example, several studies have shown that rats and monkeys reared in an isolated environment display a greater response to psychostimulant drugs when compared to animals reared in a social environment. Specifically, it has been reported that monkeys reared in isolation show an increase in psychotic-like behaviors when administered amphetamine (17), and also show increased stereotypic behaviors when given apomorphine (19). Relative to rats reared in social groups, rats reared in isolation display an increase in amphetamine-induced stereotypies (24), as well as an increase in cocaine- and amphetamine-induced locomotor behavior (5,14). Isolation-reared rats also display an enhanced sensitivity to the discriminative stimulus effects of amphetamine and cocaine compared to rats reared in an enriched social environment containing novel objects (9).

Studies assessing the influence of differential rearing on the rewarding effect of psychostimulant drugs have yielded conflicting results. For example, when given a choice between plain water or water with cocaine added, isolate-reared rats show less preference for cocaine-treated water than enriched-reared rats (12). In contrast, using the intravenous self-administration paradigm, it has been found that isolate-reared rats readily learn to take cocaine, whereas socially reared rats do not (25). A more recent study failed to find a difference between isolate- and social-reared rats in the rate of intravenous self-administration of cocaine (5).

Another study by Schenk et al. (26) has used the conditioned place preference (CPP) paradigm to assess the rewarding effects of psychostimulants in isolate- and social-reared rats. This study found that isolate-reared rats were less sensitive to the rewarding effects of cocaine than social-reared rats, a finding that appears consistent with at least one study that

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assessed cocaine self-administration in isolate- and enrich-reared animals (12). However, the study by Schenk et al. (26) did not include an enrich-reared condition for direct comparison.

The purpose of this experiment was to determine the rewarding effects of amphetamine using the CPP paradigm in rats reared in an enriched, social, or isolated environment. Numerous studies have shown that amphetamine produces CPP in rats raised in standard laboratory conditions (6,10,20). In the CPP paradigm, an animal is given a drug injection explicitly paired with one distinct environment, and a vehicle injection with a different environment. When given free-choice access to the drug- and vehicle-paired environments, the animal chooses the drug-paired environment over the vehicle-paired environment. In the present experiments, horizontal and vertical activity were also recorded during conditioning to assess the acute locomotor-stimulant effect of amphetamine in the differentially reared groups.

METHOD

Subjects and Housing Conditions

The subjects were 79 male Sprague-Dawley rats (Harlan Industries, Indianapolis, IN) received at 21 days of age. Immediately upon arrival, they were randomly placed in either an enriched (n = 28), social (n = 24), or isolated (n = 27) environmental condition. The enriched condition (EC) consisted of a large box, 94 × 94 × 51 cm high, made of plywood and painted grey. A 19 × 12 cm opening was made at the bottom center of each side and was covered with wire mesh. Through two of these openings water was continuously provided, and laboratory rodent chow (Purina) was continuously provided in food hoppers hung inside the box on the other two openings. The floor was covered with pine chip bedding, and the lid to the box consisted of wire mesh tacked to a wooden frame to provide maximum ventilation. Various objects made of metal or hard plastic were provided in the box. These objects consisted of various plastic toys (e.g., rattles, buckets, blocks, trucks, ladders) purchased from a local store, as well as junk objects such as discarded milk jugs, tubing, and old cage materials. These objects were rearranged daily, with new objects being introduced each day. The rats were removed from their box so that the objects could be replaced and moved. Fourteen rats were housed in each of two EC boxes.

The social condition (SC) consisted of a large hanging cage (24 × 40 × 18 cm high) constructed of three stainless steel solid walls, a wire mesh front wall, and a wire mesh floor. Water and chow were available ad lib. Three rats were housed in each cage, and they remained assigned to their original cage throughout conditioning and testing.

The isolated condition (IC) consisted of an individual hanging metal cage (17 × 24 × 20 cm high) constructed of three stainless steel solid walls, a wire-mesh front wall, and a wire-mesh floor. Water and chow were available ad lib. These rats were housed singly.

Both SC and IC rats were handled on three different occasions just prior to the beginning of conditioning to habituate them to handling. EC rats were handled daily when the objects were rearranged. For EC, SC, and IC animals, floor areas per animal exceeded the miniumum space recommendations for rats outlined in the Guide for the Care and Use of Laboratory Animals (NIH, 1985, Table 2-1).

Drug

Amphetamine sulfate (Sigma, St. Louis, MO) was dissolved in saline (0.9% NaCl), with dosages calculated based on the salt form of the drug. Amphetamine was injected subcutaneously at a volume of 1 ml/kg.

Apparatus

The CPP apparatus consisted of a rectangular box with three compartments made of 1/2″ plywood. The end compartments measured 24 × 30 cm × 45 cm high, with the smaller middle compartment measuring 24 × 10 cm × 45 cm high. One end compartment was painted white, had a wire mesh floor, and pine bedding beneath it. The other end compartment was painted black, had a rod floor with cedar chips beneath it. The middle compartment was painted grey and had a solid wood floor. Partitions separating the end compartments were replaceable with partitions that contained a 10 × 10 cm opening that would allow the rat free access to all three compartments. A white noise generator (ambient background of 70 dB) was also located in the same room. The CPP box was located in a room separate from the colony room. A video camera was hung directly over the apparatus to record behavior using a video monitor in an adjacent room.

Procedure

Previous work in our laboratory indicated that naive rats tend to display a slight preference for the black compartment of the apparatus. Thus, amphetamine was paired with the normally nonpreferred white compartment starting at 53 days of age. Rats from each environment were assigned to one of the treatment groups (0, 0.5, or 2.0 mg/kg amphetamine), with 8–10 subjects per drug group. Each conditioning trial took place over 2 days, and the order of conditioning was counterbalanced for rearing environment and drug condition. On the first day, half of the rats from each housing condition were injected with their respective drug and were placed individually in holding cages (individual standard hanging cages) for 10 min, then were placed in the white compartment for 20 min. The other half were injected with saline and were placed in a holding cage for 10 min, then were placed in the black compartment for 20 min. On the second day, rats that received a drug-white pairing were given a saline-black pairing, and rats previously given a saline-black pairing were given a drug-white pairing. This conditioning was continued until the rats received four conditioning trials (8 consecutive days).

In order to assess the acute locomotor effects of amphetamine during conditioning, horizontal activity (line crosses) and vertical activity (rears) were recorded for each rat's first drug pairing in white. An observer, unaware of each rat's treatment, recorded the activity, with a line cross being defined as two front paws crossing a line bisecting the compartment, and a rear being defined as two front paws leaving the floor, excluding grooming behavior. Activity was recorded according to a time-sampling procedure in which data were recorded from minutes 0–4, 8–12, and 16–20 of the 20-min conditioning trial.

On the day immediately following the last conditioning day, each rat received a 10-min preference test while in a drug-free state. Partitions in the apparatus were replaced with partitions containing an opening to allow free access to the entire apparatus. The rat was placed in the middle grey compartment to begin the test. An observer, unaware of the rat's individual treatment, recorded the duration spent in the white and black compartments, as well as the number of entries into white and black. An entry was defined as two front paws crossing into the respective compartment. A second test day was conducted 24 h later in exactly the same manner as the

TABLE 1

NUMBER OF LINE CROSSES AND REARS ON CONDITIONING DAY 1 IN THE WHITE COMPARTMENT FOR SALINE-INJECTED CONTROLS FROM EACH ENVIRONMENTAL CONDITION

Environment	n	Line Crosses	Rears
EC	8	24.5 ± 3.7	22.5 ± 2.5*
SC	8	33.4 ± 2.8	29.9 ± 3.7
IC	9	34.3 ± 3.6	35.1 ± 2.6

Values represent mean ± SEM.
*Significant difference from the IC group, $p < 0.05$.

first test, with durations and entries into white and black being recorded.

Data Analysis

To assess the effects of the environmental treatment alone, control (saline-treated) values from EC, SC, and IC animals on conditioning day 1 in the white compartment were analyzed using a separate ANOVA for the number of line crosses and the number of rears. The duration data across test days 1 and 2 were also analyzed from control animals, using a separate ANOVA for the duration in the white, black and grey compartments. For each dependent measure, a Tukey's HSD test was used for post hoc analyses whenever the main effect of environment was significant. Statistical significance was declared at $p < 0.05$.

To assess drug effects within each environmental condition, data for all drug-treated groups were transformed to a percent change from saline control. Individual raw scores were calculated to be a percent change from the mean control value for the appropriate environmental condition. This data transformation was conducted to equate the control (saline) measures within each environmental condition, as has been suggested previously (5). The percent change from control for line crosses and rears on conditioning day 1, as well as duration in white on test days 1 and 2, were then analyzed by 2 × 3 ANOVAs, with two levels of drug dose (0.5 and 2.0 mg/kg) and three levels of environment (EC, SC, and IC). Post hoc comparisons were made using a Newman-Keuls test, and significance was declared at $p < 0.05$.

RESULTS

Effect of Environment in Saline Controls

As shown in Table 1, on conditioning day 1 in the white compartment, there were no significant differences among control groups in line crosses. However, the EC group showed decreased rearing compared to the IC group, $F(2, 22) = 4.70$, $p < 0.05$.

As shown in Table 2, on test days 1 and 2, overall analyses in saline controls indicated no significant differences among EC, SC, and IC rats for duration in the white or grey compartments. There was a significant difference between EC and IC rats for duration in the black compartment on test day 1, $F(2, 23) = 6.21$, $p < 0.05$, but not on test day 2. Regardless of environmental condition, rats preferred the smaller middle grey compartment relative to both the white and black end compartments.

Amphetamine-Stimulated Locomotion

The overall ANOVA for horizontal line crosses on conditioning day 1 in amphetamine-treated rats yielded a significant main effect of environment, $F(2, 46) = 21.46$, $p < 0.001$. Comparisons across environmental conditions showed that both doses of amphetamine (0.5 and 2.0 mg/kg) increased line crosses significantly more in EC rats than in IC rats (see Fig. 1). Additionally, 0.5 mg/kg amphetamine increased line crosses more in EC rats than in SC rats.

The overall ANOVA for vertical rears produced significant main effects of environment, $F(2, 46) = 15.12$, $p < 0.001$ and amphetamine dose, $F(1, 46) = 9.24$, $p < 0.01$. As illustrated in Fig. 2, both amphetamine doses caused a greater increase in rearing in EC rats than in IC rats. Also, 0.5 mg/kg amphetamine increased rearing more in EC rats than in SC rats.

Amphetamine-Conditioned Place Preference

The overall analysis for percent change from control on test day 1 yielded significant main effects of environment, $F(2, 47) = 6.10$, $p < 0.01$, and amphetamine dose, $F(1, 47)$

TABLE 2

DURATION SPENT IN THE WHITE, BLACK AND GREY COMPARTMENTS ON TEST DAYS 1 AND 2 FOR SALINE-INJECTED CONTROLS FROM EACH ENVIRONMENTAL CONDITION

Environment	n	White	Black	Grey
		Test Day 1		
EC	8	135 ± 17	182 ± 14*	283 ± 16
SC	8	142 ± 8	166 ± 11	292 ± 11
IC	9	154 ± 16	122 ± 12	324 ± 16
		Test Day 2		
EC	8	99 ± 11	143 ± 18	357 ± 26
SC	8	138 ± 11	155 ± 15	307 ± 13
IC	9	128 ± 11	155 ± 12	317 ± 13

Values represent mean ± SEM.
*Significant difference from the IC group, $p < 0.05$.

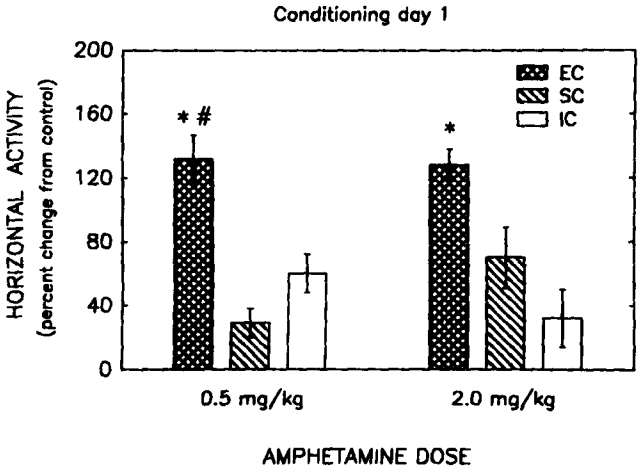

FIG. 1. Amphetamine-induced horizontal activity in EC, SC, and IC rats on conditioning day 1. Each value represents the mean (±SEM) number of horizontal line crosses expressed as a percent change from saline-injected control animals within the same environmental condition. Asterisk (*) represents significant difference from the IC group and crosshatch (#) represents significant difference from the SC group, $p < 0.05$.

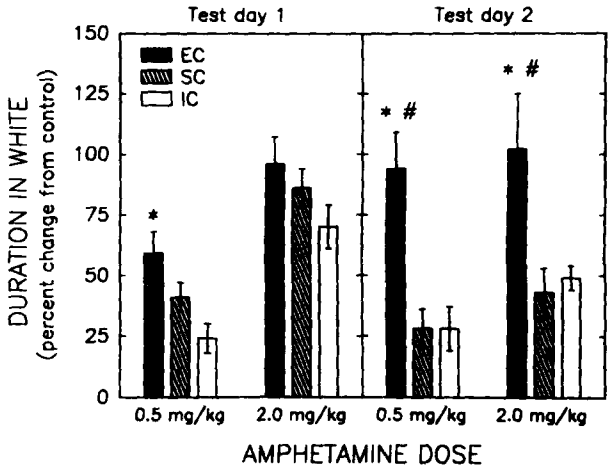

FIG. 3. Amphetamine-induced conditioned place preference in EC, SC, and IC rats on test days 1 and 2. Each value represents the mean (±SEM) duration spent in the drug-paired white compartment expressed as a percent change from saline-injected control animals within the same environmental condition. Asterisk (*) represents significant difference from the IC group and crosshatch (#) represents significant difference from the SC group, $p < 0.05$.

= 33.64, $p < 0.001$. Comparison across environmental conditions showed that 0.5 mg/kg amphetamine produced a significantly greater CPP in EC rats than in IC rats, as illustrated in Fig. 3. The main effect of amphetamine dose indicates that the strength of the CPP increased for the 2.0 mg/kg dose compared to the 0.5 mg/kg dose for all environmental conditions.

The overall analysis for drug-treated rats on test day 2 yielded only a significant main effect of environment, $F(2, 46) = 12.12$, $p < 0.001$. Subsequent post hoc comparisons showed that both amphetamine doses produced a greater CPP in EC rats compared to SC and IC rats (Fig. 3, right panel).

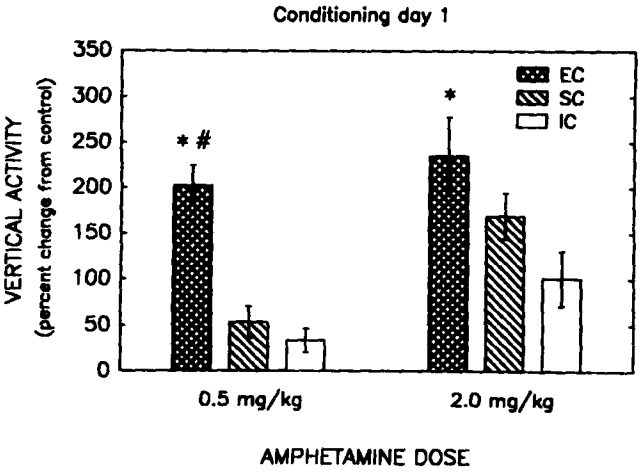

FIG. 2. Amphetamine-induced vertical activity in EC, SC, and IC rats on conditioning day 1. Each value represents the mean (±SEM) number of vertical rears expressed as a percent change from saline-injected control animals within the same environmental condition. Asterisk (*) represents significant difference from the IC group and cross-hatch (#) represents significant difference from the SC group, $p < 0.05$.

DISCUSSION

The results indicate that EC animals were more reactive than IC animals to the acute locomotor effects of amphetamine at both doses tested (0.5 and 2.0 mg/kg), and more reactive than SC animals at the lowest dose. This is consistent with at least one other previous report that compared the locomotor stimulant effects of amphetamine in EC and IC rats (4). Similar to the locomotor effects, EC animals in the present study were more sensitive than IC and SC animals to the rewarding effects of amphetamine measured by CPP. Although conflicting evidence exists, this latter finding is consistent with at least one other report showing oral self-administration of cocaine is greater in EC rats than IC rats (12).

One possible explanation for the enhanced effect of amphetamine in EC animals is that the EC environment may alter brain pathways important in mediating the effects of amphetamine. It is well documented that rats raised in an enriched environment display a decreased neural density and a concomitant increase in glia and number of dendritic spines in areas of the cortex (8,11). While subcortical differences are not definitely known, recent research from our laboratory has shown that the mesolimbic and nigrostriatal dopamine systems, which release dopamine in response to amphetamine, are altered by the EC environment (4). Perhaps the novel stimuli and social interaction provided by the EC environment acts on these pathways, and sensitizes them to the acute effects of amphetamine.

In support of this, novel environmental stimuli, which are present in the EC environment, are thought to activate the dopaminergic mesolimbic pathway (1,23). Perhaps daily presentations of novel stimuli sensitizes the dopaminergic mesolimbic system, not unlike a low dose of amphetamine (16,18).

For example, it has been shown that locomotion can increase DA activity in the nigrostriatal and mesolimbic DA system (2), and perhaps this may account for the sensitizing effects of the EC environment. Additionally, certain environmental conditions known to activate the mesolimbic dopamine system can cross-sensitize rats such that subsequent administrations of amphetamine are enhanced (22).

In the present study, there are at least two different factors that may account for the enhanced amphetamine-induced locomotion and reward observed in EC rats relative to IC. One possibility is that differences among environmental groups may be explained by changes in drug bioavailability. For example, because EC rats have smaller livers than IC rats (3), EC rats may metabolize amphetamine slower than IC rats. In addition, it has been shown that the size of cerebral capillaries is increased in EC rats relative to IC (27). This could allow more drug to affect the brain of EC rats. Consistent with this, it has been determined that, relative to IC rats, EC rats show an enhanced neurochemical (DA) response to amphetamine that is administered peripherally, but not to amphetamine that is administered in an in vitro slice preparation (4).

Another possibility for the enhanced response to amphetamine in EC rats is that some pharmacodynamic change independent of drug bioavailability may have been induced by the environmental treatment. Indeed, direct injection of amphetamine into the nucleus accumbens has been shown to have different behavioral effects in SC and IC rats (15), which cannot be readily explained by changes in drug bioavailability. Perhaps alterations in synaptic density may contribute to the differential response to amphetamine. In the occipital cortex, EC rats have more synapses per neuron than IC rats (27). If there is also an increase in synaptic density in the mesolimbic DA system, where amphetamine acts as an indirect agonist that stimulates DA release (13), then this may enhance amphetamine's ability to activate postsynaptic neurons.

Regardless of the mechanism, however, the present results seem somewhat unexpected when viewed within the context of a previous study examining individual differences in response to amphetamine (21). In that previous study, individual rats from a general population were categorized as either low or high responders, based upon their rate of locomotor activity in an inescapable novel environment. High responders were shown to be more sensitive to the locomotor-stimulant and rewarding effects of amphetamine than low responsers. This contrasts with the finding that IC rats, which may be categorized as high responders, based upon their increased horizontal and vertical activity in a novel environment relative to EC rats [(4,15), and see Table 1 of present report], displayed a reduced response to amphetamine relative to EC rats. Thus, it appears that predicting individual differences in sensitivity to amphetamine based upon individual differences in locomotor activity in a novel environment may not generalize to a situation where animals receive differential treatment during development.

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