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Housing Conditions Fail to Affect the Intravenous Self-Administration of Amphetamine

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SCHENK, S., B. ROBINSON AND Z. AMIT. *Housing conditions fail to affect the intravenous self-administration of amphetamine.* PHARMACOL BIOCHEM BEHAV 31(1) 59–62, 1988.—Rats were housed either in isolation or in groups of 4 for 6 weeks following weaning (21 days). After this housing period, some of the rats were tested for the acquisition of intravenous self-administration of amphetamine (0.004–0.25 mg/kg/infusion) and others were tested for the locomotor activating effects of amphetamine (0–1.0 mg/kg, IP). In the self-administration tests, both the isolated and grouped rats readily acquired the operant to obtain drug infusions and exhibited dose-dependent behavior. These results are in direct contrast to those we have obtained concerning the influence of the environmental manipulation on cocaine self-administration. In those tests, only isolated rats self-administered cocaine. The results of the locomotor tests indicated that whereas the isolated rats were consistently more active, the dose/response curves for the effects of amphetamine on activity were parallel for the rats reared under the different housing conditions. Thus the environment has specific effects on behavior which may be a reflection of specific neurochemical effects of the manipulation.

Self-administration Stimulants Amphetamine Housing Locomotion Environment

RECENTLY, we have reported that the intravenous self-administration of cocaine in laboratory rats is markedly modified by early housing conditions (14). "Isolation housed" rats readily self-administered cocaine while rats that had been group-housed for a 6 week period from weaning failed to self-administer this drug. The behavior of the isolated rats was dose-dependent and thus could not be easily explained by the idea that they were simply more active than their group housed counterparts. Since a large range of doses were tested and the grouped rats failed to self-administer cocaine reliably, we interpreted the differences as due to a difference in the sensitivity of these rats to the positively reinforcing properties of cocaine. One explanation for the behavioral differences between the differentially housed rats was that early housing conditions altered the development of relevant neural systems for the expression of the rewarding properties of cocaine.

Recent evidence suggests that the rewarding effects of different drugs of abuse may be mediated via the activation of different neural circuits. It has been suggested that cocaine reinforcement is derived from the action of the drug on the mesocortical dopamine system. This hypothesis is based on the results of intracranial self-administration studies. Cocaine in those studies was infused directly and exclusively into the medial prefrontal cortex (4). The resulting self-administration was dose-dependent and a pharmacological profile of the behavior indicated a specific dopaminergic mechanism (5,6). In contrast, an abundance of empirical support for the view that cocaine self-administration is dependent on activity in the mesolimbic dopamine system is also available (11–13, 18). The discrepancy in the literature concerning the role of the prefrontal cortex in the rewarding properties of cocaine may be attributable to a difference in the variables being measured. On the one hand, *acquisition* of cocaine self-administration may rely on an intact mesocortical dopamine system whereas *maintenance* of the behavior may rely on the mesolimbic dopamine system.

The bulk of evidence supports the notion that the reinforcing properties of amphetamine may also rely on an intact mesolimbic dopamine system. Self-administration of amphetamine has been reported when the drug is injected directly into tissue in the nucleus accumbens (7) and the intravenous self-administration of amphetamine is attenuated by neurotoxin lesions into the nucleus accumbens (9) or with neuroleptics (16,17). Thus, the mesolimbic dopamine system seems important for both the *acquisition* and the *maintenance* of amphetamine self-administration. However, a potential role for other neurochemical systems in the reinforc-

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ing properties of amphetamine has not yet been systematically investigated. For example, a role for the prefrontal cortex also seems possible particularly in light of the demonstration of self-administration of amphetamine directly into the orbitofrontal cortex by rhesus monkeys (10) even though neurotoxic lesions to the dopamine terminals in the medial prefrontal cortex failed to alter the acquisition or maintenance of intravenous amphetamine self-administration by rats (8).

The present experiment is an examination of the specificity of the housing manipulation by assessing the effect of early environment on amphetamine self-administration and hyperactivity.

METHOD

Subjects

Subjects were male Long Evans rats obtained at weaning (21±2 days of age). They were housed in hanging stainless steel cages either in isolation (cage size=20×25×18 cm) or groups of 4 (cage size=41×25×18 cm) for 6 weeks postweaning. Food and water were freely available at all times except during testing. The rats were kept in an animal colony with lights on at 0800 and off at 2000 hr.

Self-Administration

Each rat was implanted with a chronic indwelling jugular catheter according to a modified version of Weeks (15). The catheter line was passed subcutaneously and mounted on top of the rats head with dental acrylic anchored to 4 stainless steel jewellers screws embedded in the skull. Following the surgical manipulation, the rats were returned to their housing conditions and permitted 7 days recovery. The catheter lines were flushed daily with 0.1 ml saline/heparin/penicillin solution to minimize infection and the formation of blood clots.

Following recovery from surgery, the rats were introduced to a standard operant chamber equipped with a lever which, when depressed, activated a motorized pump (Razel) that delivered 0.1 ml drug solution through the catheter line. A cue light was also activated during the infusion (12 sec). A chart recorder recorded the occurrence of reinforced lever presses. Test sessions were of 3 hr duration. The initial dose of amphetamine was 0.25 mg/kg/infusion. The rats were maintained on this dose for an initial 4 days after which the unit dose was repeatedly reduced by half every 2–4 days. Thus, the range of doses that was tested was 0.004–0.25 mg/kg/infusion during a period of 15 days.

During the course of the experiment, a number of rats from both housing conditions either dislodged the head assembly or developed blockages or leaks of the catheter lines (4 isolated and 4 grouped rats). Data analysis was performed on the results of the remaining 13 isolated and 8 grouped rats that completed the experiment.

Locomotor Effects

Additional 63 rats (32 grouped and 31 isolated) were given an intraperitoneal injection of amphetamine SO_4 (0, 0.25, 0.5 or 1.0 mg/kg) dissolved in physiological saline and introduced to open field boxes (45.7×45.7×39.4 cm). Each box was painted black and was illuminated by a 40-watt incandescent bulb placed 80 cm above the center of the floor. There were 4 sets of light sources and photocells located 3.8 cm above the floor of the chamber. These were arranged so that a pair of light beams crossed the other pair perpendicularly, dividing the chamber into 9 sections. Each time the rat interrupted one of the beams, it was automatically recorded as a count in an adjacent laboratory. Test duration was 90 min.

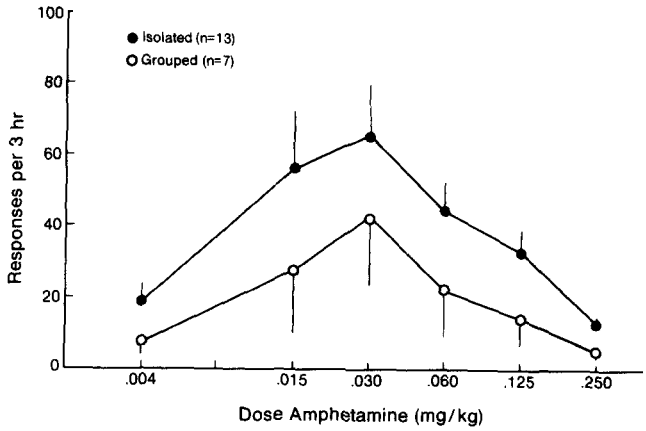

FIG. 1. Total responses per 3 hours for the isolated and grouped rats. The shape of the dose-response curve for the two groups of rats does not differ although the curve of the isolated rats is displaced vertically relative to their grouped housed counterparts. Symbols represent the means. Vertical bars represent the standard error of the mean.

RESULTS

Self-Administration

Figure 1 shows the total number of responses as a function of dose of amphetamine for the grouped and isolated rats. The data have been collapsed across days for each dose. Thus each data point represents the average responses for each dose for the 2–4 days of testing at that dose.

Both the isolated and grouped rats exhibited a dose-dependent response rate. The dose/response curve is in the shape of an inverted U with maximal rates obtained with the 0.03 mg/kg/infusion dose. Both higher and lower doses produced a decrease in response rates. A two-way repeated measures ANOVA (housing × dose) was performed on the data. Results indicated that although the isolated rats tended to have higher response rates than the aggregated rats, the effect of housing was not significant, $F(1,19)=3.80$, $p>0.05$. Neither was the interaction of housing with dose significant, $F(5,95)=1.29$, NS. Only the dose effect was statistically reliable, $F(5,95)=5.42$, $p<0.01$. Thus, housing did not influence the propensity of rats to self-administer amphetamine.

Some rats (6 isolated and 4 grouped) were subsequently tested with saline substituted for the amphetamine solution. Responses for saline infusions were comparable to the 0.004 mg/kg dose (mean of 2 days: isolated=18; grouped=6.9). However, when 0.06 mg/kg/infusion was again available, response rates increased (mean rates: isolated=66; grouped=24.8). Thus the behavior was under the control of the dose of amphetamine.

Hyperactivity

Figure 2 shows the total locomotor counts for the isolated and grouped rats given the various doses of amphetamine. Although there was a tendency for the isolated rats to be hyperactive, as indicated by their overall higher locomotor

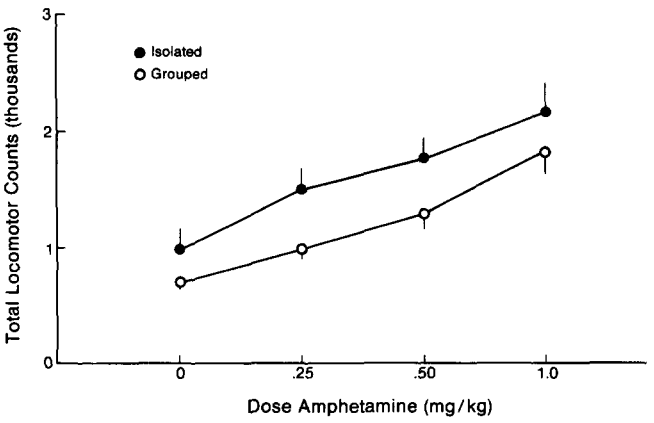

FIG. 2. Total locomotor counts for grouped and isolated rats treated with various doses of amphetamine. Symbols represent the mean score. Vertical bars represent the standard error of the mean.

scores, the dose/response curves for rats reared under the two housing conditions were parallel. A two-way ANOVA (housing × dose) revealed a significant effect of dose, $F(3,55)=16.26$, $p<0.01$, and housing, $F(1,55)=10.73$, $p<0.01$, but no significant interactions between housing and dose, $F(3,55)=0.19$, NS.

DISCUSSION

Housing conditions that influenced cocaine self-administration so significantly (14) failed to alter amphetamine self-administration. Thus, for cocaine self-administration we have demonstrated that a high risk group for this behavior can be experimentally produced. The same does not seem to hold for amphetamine self-administration. This behavior does not appear to come under the control of the same environmental factors that have been demonstrated to predispose animals to the rewarding properties of cocaine. Thus, the data support the notion that the acquisition of self-administration of cocaine and amphetamine is mediated by distinct neurochemical systems that are differentially sensitive to housing conditions.

The effects of the housing manipulation on locomotor behavior indicated that the isolated rats were hyperactive relative to the aggregated rats. Activity levels were consistently higher for isolation housed rats. The response to amphetamine in the differentially housed rats did not, however, differ with housing, as indicated by the parallel dose/response curves for rats reared under the two conditions.

These activating effects of amphetamine have been linked to the effects of the drug on mesolimbic dopamine neurons (3,16). The parallel dose/response curves for the effects of amphetamine in the differentially housed rats would argue against the hypothesis that housing produces differences in receptor affinity or in the ability for amphetamine to block the reuptake or release of dopamine. However, the higher level of activity in isolated rats would suggest that either postsynaptic receptor density is higher or that another neurochemical effect of the housing is responsible for the hyperactivity produced by isolation.

The behavioral data collected thus far are consistent with the notion that housing conditions alter the development of specific neurochemical systems resulting in different responses to only some drugs as measured in only some behavioral paradigms. The basis for these differences will require biochemical investigations to assess (1) binding characteristics of specific dopaminergic systems in differentially housed rats and (2) dopaminergic activity in specific central systems of the housed rats.

It is important to compare the housing conditions manipulated in the present study and in our previous work (14) to the more typical conditions that have become the standard in self-administration experiments. Rats are typically obtained from the breeding farms at approximately 3–6 weeks postweaning. Prior to their introduction to research laboratories, the rats are housed in aggregated conditions. Usually, either upon arrival at the research institute or following a surgical manipulation, the housing is changed to an isolated condition. Thus, the "typical" lab rat is initially housed in a group and thereafter is housed in isolation. This condition is not the same as the conditions that we have used to induce a high percentage of cocaine using rats (chronic isolation from weaning) or those that inhibit cocaine self-administration (chronic grouping from weaning). In spite of the differences between our housing conditions and those that are more typically imposed, the number of rats that learn to self-administer cocaine is generally considered to be equally high regardless of whether rats are housed chronically in isolation (14) or initially grouped and then isolated as is the more common practice.

These findings would suggest that a period of isolation housing, even following an extended period of grouping, is sufficient to increase the probability of drug-taking in laboratory animals. This has been found for morphine self-administration. Rats initially housed in groups and subsequently housed in isolation consumed greater quantities of morphine solution than rats that were never exposed to isolated conditions (1). Similarly, we have found that a large percentage of initially group housed rats, if subsequently isolated, will also learn to self-administer cocaine (Schenk, Boyle and Amit, in preparation). Thus, a period of isolation, *even in adulthood,* may suffice to increase the sensitivity of rats to cocaine reward. This notion and possible mechanisms for the housing effect are currently being investigated in our laboratory.

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