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BRIEF COMMUNICATION

Differential Effects of Isolation Housing on the Conditioned Place Preference Produced by Cocaine and Amphetamine

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SCHENK, S., T. HUNT, R. MALOVECHKO, A. ROBERTSON, G. KLUKOWSKI AND Z. AMIT. *Differential effects of isolation housing on the conditioned place preference produced by cocaine and amphetamine.* PHARMACOL BIOCHEM BEHAV **24**(6) 1793–1796, 1986.—Rats were obtained at 21 days of age and were housed either in isolation or in groups of 4 for 6 weeks. They were then tested for their sensitivity to cocaine HCl (0.31, 0.62, 1.25 or 2.5 mg/kg) or d-amphetamine SO_4 (0.031, 0.062, 0.125, 0.25 or 0.5 mg/kg) using a modified place preference paradigm. The isolated rats were insensitive to cocaine in this paradigm whereas the group-housed animals showed peak effects at the lowest dose of this drug. In contrast, there was no difference in sensitivity to amphetamine as a function of housing conditions. These data strengthen the notion that the effects of the early environment on drug sensitivity in the adult are specific to certain classes of drugs. Further, these data lend support to the notion that the effects of cocaine and amphetamine in the place preference paradigm are mediated by different neural systems.

Housing Cocaine Amphetamine Conditioning Place preference

MANY of the behavioral effects of drugs of abuse are characterized by large across-subject variability. It is possible that this observed variability represents an inherent difference that exists between rats that causes some to be more sensitive to these drugs than others. If so, an understanding of the factors that contribute to the subject variability will inevitably lead to an understanding, at least in part, of the factors that contribute to drug abuse in general.

Housing conditions can alter the sensitivity to exogenously administered opiates. Rats that are housed in isolation are less sensitive to opiate-produced analgesia [5] and conditioned place preference [7,8], show a less severe opiate withdrawal syndrome [1] and orally consume greater quantities of morphine solution [2] than rats that are group housed. Further, the differences may be the result of developmental factors since isolation in the adult fails to decrease the sensitivity of rats to heroin [8] whereas it is quite effective when performed immediately post-weaning [7,8]. The early social environment may therefore be one of the critical factors that determines the behavioral sensitivity of an adult animal to opiates.

The present study extends these findings by examining the generality in this housing effect on sensitivity to dependence-inducing drugs. Neurochemical investigations have revealed that the activity of mesocortical-frontal but not mesolimbic or nigro-striatal dopamine neurons is reduced in isolated rats [3]. It is possible that some of the behavioral effects of isolation housing are a result of this specific effect on central dopaminergic activity. One way to test this hypothesis is to assess the sensitivity of differentially housed animals to drugs that act specifically on either the mesolimbic or mesocortical dopamine system.

The conditioned place preference produced by cocaine is suggested to be mediated by the activation of the mesocortical dopamine system [4]. The amphetamine-produced conditioned place preference seems to be mediated by the activation of the mesolimbic system [10]. In the present study, we examine the effects of different environmental rearing conditions on the conditioned place preference produced by these two psychomotor stimulants.

METHOD

Subjects

Subjects were 166 male Long-Evans rats obtained at 21 days of age, immediately post-weanining (Canadian Breed-

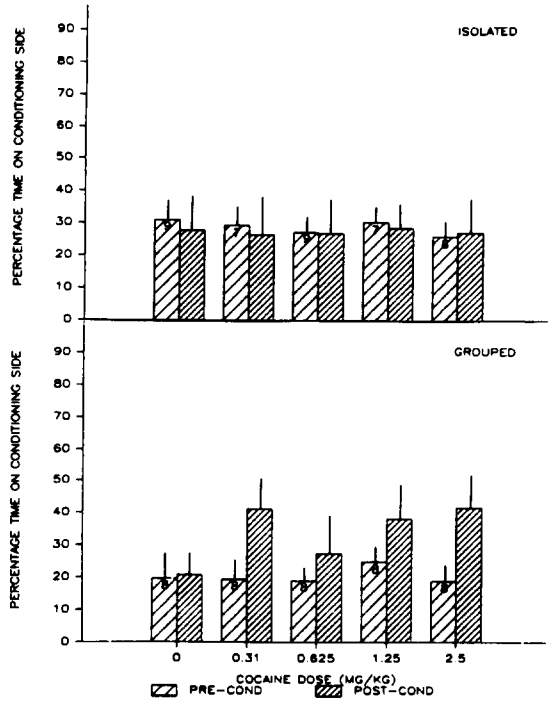

FIG. 1. Mean percentage time (+SEM) spent in the initially non-preferred environment before and after conditioning with cocaine HCl for group- and isolation-housed rats. Numbers in the bars represent sample sizes.

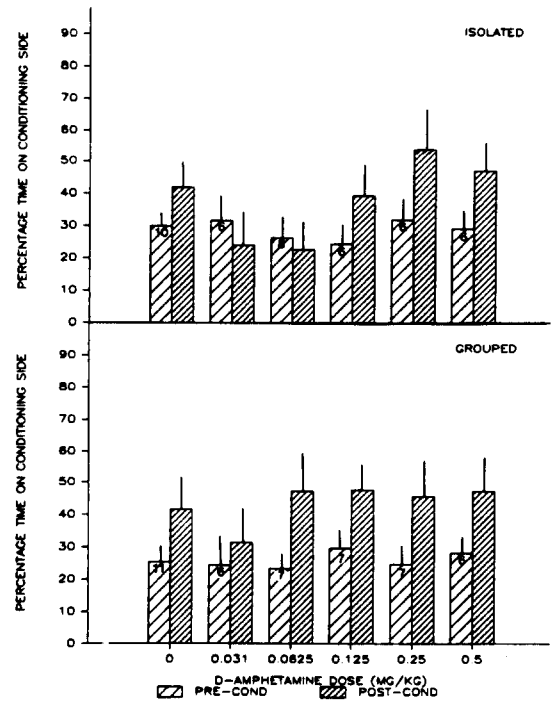

FIG. 2. Mean percentage time (+SEM) spent in the initially non-preferred environment before and after conditioning with d-amphetamine SO_4 for group- and isolation-housed rats. Numbers in the bars represent sample sizes.

ing Farms Ltd., St. Constant, Quebec). They were randomly divided into either the isolated (n=82) (20×25×18 cm cage) or aggregated conditions (n=84) (4 per metal cage) (41×25×18 cm). These housing conditions were maintained for 6 weeks with food and water freely available. Accordingly, the rats were 63 days of age when the actual experiment began. The rats were kept on a 12:12 hour (lights on at 0700 hr and off at 1900) light:dark cycle.

Apparatus

Eight testing chambers were used. Each consisted of a plywood box (56.5×12.5×30 cm) with a removable lucite top. Each box was divided into two distinct sections. On one side the floor was constructed of plywood wrapped in wire mesh and the walls were made of metal. On the other side, the floor was made of plain plywood and the walls were made of plywood painted with black stripes. The floor of each box was balanced on a central dowel which allowed the floor to tip if the weight was unevenly distributed. Located underneath the floor, on one side, was a microswitch which, when depressed, activated a timing mechanism.

Procedure

The experiment consisted of three phases. During all phases, testing was carried out between 13:00 and 16:00 hr under low level lighting conditions.

Habituation (4 days). During this phase, the rats were permitted free access to the entire testing chamber for 15 minutes per day. The amount of time spent on each side of the testing chamber was recorded. The average time spent in each compartment of the box on the last two habituation days was determined for each rat and served as the preconditioning baseline score.

Conditioning (4 days). During this phase, the rats were given a daily subcutaneous injection of either a vehicle solution, cocaine HCl (0.31, 0.63, 1.25, or 2.5 mg/kg) or d-amphetamine SO_4 (0.031, 0.063, 0.125, 0.25 or 0.5 mg/kg). The doses used in the present study were derived from pilot work in our laboratory as well as from the results of Spyraki *et al.*, [9,10] pertaining to the conditioned place preference produced by psychomotor stimulants. In these studies, 2.5 mg/kg cocaine [9] and 0.5 mg/kg d-amphetamine [10] were the lowest doses to produce a reliable place preference. Our pilot data confirmed this and further indicated that approximately 80% of the rats administered these drug doses showed an increase in the percentage time spent in the environment in which the rats experienced the drug effects. As the dose was decreased, we found that the percentage of rats showing the increase in time also decreased to the level of saline controls (at 0.625 mg/kg cocaine and 0.25 mg/kg amphetamine). We therefore decided to test the drug doses that exhibited the most variability as well as a dose that had been found to produce reliable effects. In this manner, we expected to maximize the probability of observing differential sensitivity as a function of housing. It is likely that higher doses would produce more substantial place preference effects. However, we were most interested in assessing the effects of housing conditions on sensitivity to psychomotor stimulants, an investigation that required the use of doses at the low end of the dose/response curve.

Immediately following the injection, the rats were con-

fined to the side of the apparatus that they initially found to be non-preferred for 15 min per day (for group sizes refer to Figs. 1 and 2).

Test day (1 day). The rats were given an injection of vehicle solution and again allowed free access to the entire testing chamber for 15 min. The amount of time spent in the conditioned compartment was recorded and compared to the amount of time spent in that compartment pre-conditioning.

All drugs were dissolved in physiological saline in a concentration such that injections were in a volume of 1 ml/kg.

RESULTS

Figure 1 shows the percentage of time spent on the conditioned (initially non-preferred) side of the test chamber before and after conditioning with cocaine. A 3-way ANOVA (Dose × Housing × Days) performed on the percentage time in the conditioned environment yielded a significant interaction between Days and housing, $F(1,70)=5.425$, $p=0.021$. It is apparent that the isolated rats did not increase the percentage of time spent on the conditioned side of the chamber even at the highest dose tested (2.5 mg/kg). In contrast, increases in the percentage time spent in the conditioned environment are seen in the group-housed rats at the lowest dose tested (0.31 mg/kg). The lack of a dose/response curve, as indicated by the failure to find a main effect of drug dose, makes further post-hoc comparisons impossible.

Figure 2 represents the amount of time spent in the conditioned environment before and after conditioning with amphetamine for the group and isolation housed rats. A 3-way ANOVA on the percentage time spent in the conditioned environment (days × dose × housing condition) yielded only a significant effect of days, $F(1,74)=15.42$, $p<0.001$. Thus housing conditions did not influence the effects of amphetamine in this paradigm.

It should be pointed out that there is a substantial increase in the percentage time spent in the environment in which the rats received *vehicle* injections, an unfortunate effect that requires some elaboration. In our hands, this non-pharmacological effect is the exception rather than the rule. We have now published data from 5 control groups [7,8] and have tested approximately 20 such groups. To date we have only observed the "vehicle effect" reported in this study. Since (a) low doses of amphetamine fail to produce similar shifts, and (b) the increases in percentage time systematically increase with dose in the isolated rats, the "vehicle effect" is most likely a spurious result that should not preclude the interpretation of the effects of the housing manipulation on amphetamine sensitivity.

DISCUSSION

Animals housed in isolation immediately post-weaning were less sensitive to cocaine than were animals housed in aggregation. The rats were virtually insensitive to cocaine after being reared in social isolation. It is possible that the difference in sensitivity to cocaine is a reflection of non-specific effects of the manipulation. For example, isolation housed animals are generally more active than their group housed counterparts [6,12]. Differences in activity could possibly prevent some rats from exhibiting a conditioned place preference due to inattentiveness to the environmental cues. However, this interpretation of the data is unlikely since rats housed in the same manner still show a place preference to amphetamine (this experiment) and to heroin, although the dose/response curve for heroin effect is shifted to the right [7,8] of the group housed rats. Within this context it is interesting to note that it has been suggested that a place preference to amphetamine is related to its ability to enhance locomotion [11]. If so, we may have expected the isolation-housed "hyperactive" rats to show an enhanced amphetamine-induced, and possibly cocaine-induced, place preference. Clearly this was not the case. Had higher doses than those in the present study been used, an effect may have been observed in the isolated rats.

That the response to amphetamine was not influenced by the housing manipulation suggests that the mature rat's response to specific drugs of abuse is influenced by its early social environment. If so, it is interesting to consider that the same housing manipulation now shown to dramatically alter cocaine sensitivity, moderately alters heroin sensitivity [6,7] but apparently has little or no effect on amphetamine sensitivity as measured in the conditioned place preference paradigm. This suggests that the early social environment may influence specific neurochemical systems in the developing nervous system thus differentially affecting the adult rat's sensitivity to dependence-inducing drugs.

A candidate for these behavioral effects of the housing manipulation is the mesocortical dopamine system which has been suggested to mediate the cocaine CPP [4]. The decreased sensitivity of isolated rats to cocaine may well be a reflection of decreased dopamine activity in the prefrontal cortex resulting from the housing manipulation [3]. The notion of a specific dopaminergic effect is further supported by the failure to find a difference in amphetamine CPP with the housing manipulation. This behavior has been suggested to be mediated by the mesolimbic DA system [10] which is unaffected by isolation housing [3].

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