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Influence of Housing Conditions on the Acquisition of Intravenous Heroin and Cocaine Self-Administration in Rats

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BOZARTH, M. A., A. MURRAY AND R. A. WISE. *Influence of housing conditions on the acquisition of intravenous heroin and cocaine self-administration in rats*. PHARMACOL BIOCHEM BEHAV 33(4) 903–907, 1989.—Group-housed and individually housed rats were tested for the acquisition of a lever-pressing response reinforced by intravenous heroin or cocaine; animals in each housing condition quickly learned to self-administer drug. In the first experiment the isolated rats learned to self-administer heroin earlier than the group-housed animals, but the two groups self-administered similar levels of heroin by the fifth week of testing. In the second experiment cocaine self-administration was learned with equal speed in the two groups, and similar levels of cocaine were self-administered by both groups throughout the experiment. These data indicate that while social isolation can influence levels of heroin self-administration, isolation is not a necessary condition for heroin or cocaine injections to be reinforcing.

Drug addiction Cocaine Drug-taking behavior Grouped housing Heroin Intravenous self-administration Isolated housing

ALTHOUGH only a small portion of the human population develops problems with drug addiction, lower animals seem universally susceptible to the reinforcing effects of such drugs as heroin, amphetamine, and cocaine [see (17)]. One view is that such drugs are potentially dangerous for all individuals, but most humans avoid addiction because they are capable of anticipating the adverse consequences of drug-taking behavior. Another view is that the conditions of human society make only some individuals susceptible to drugs and that special conditions of the laboratory account for the high susceptibility of laboratory animals. In particular, it has been suggested that conditions of social isolation make both humans and laboratory animals susceptible to opiate addiction (1, 4, 12). This notion fits well with evidence linking endogenous opioid peptides to aspects of social attachment; pharmacological blockade of endogenous opioid peptides causes grouped animals to give distress cries normally associated with social isolation, while morphine relieves such cries even when the animals are maintained in isolation (10, 11, 13, 14).

The hypothesis that social isolation is a necessary condition for opiate addiction has received empirical support from a series of studies showing that group-housed animals orally self-administer very little morphine, while animals maintained in an isolated-housing condition drink significant quantities of morphine solution (2, 3, 9). Alexander and his co-workers have tested rats for voluntary oral self-administration of a sweetened morphine solution. Some animals are housed in a grouped condition where 16 to 22 rats live in a 8.8 m^2 enclosure. Other animals are housed in an isolated condition using individual rat cages that are commonly used in laboratory research. Animals housed in the grouped condition drink very little morphine solution, while animals that are housed in the isolated condition drink significant quantities of morphine solution. Several variations of this basic experiment have been reported, and consistent differences between grouped and isolated rats have been found. This has prompted Alexander to boldly suggest "rats housed in quasi-normal conditions have very little appetite for opiates" [p. 87, (1)].

The question of whether mere exposure to opiates puts an individual at risk for addiction, regardless of the richness of that individual's social environment, is an important question and merits further investigation. The previous work using oral morphine self-administration has two potential problems. First, the interpretation of oral self-administration studies has been challenged by some investigators [see (8)], and intravenous self-administration offers a less controversial measure of drug reinforce-

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ment. Second, group-housing conditions may affect availability of drug for individual animals. Dominant animals may block access to the drinking tube containing the drug and thus a single rat may consume the morphine solution and prevent other rats from drinking.

Some authors have suggested that addictive drugs are reinforcing because they pharmacologically activate brain systems involved in reward processes (5, 6, 15, 16). This model suggests that no preexisting factors are necessary for a drug to be reinforcing (5)—addictive drugs are seen as directly activating brain systems involved in motivation and reward and are thus potentially reinforcing for any organism. Other authors have suggested that preexisting conditions are necessary for a drug to be reinforcing [see (4)]; this alternative model postulates that drugs are reinforcing only in animals that have certain preexisting factors that are specific to the organism's history. This hypothesis implies that drug self-administration in laboratory animals is essentially an "artifact" of the experimental conditions and that drug self-administration does not involve the pharmacological activation of brain systems normally involved in reward and motivation.

Because the potential influence of housing conditions on drug-taking behavior has important implications for understanding the basis of drug reinforcement, two experiments were conducted to assess the influence of this variable. In the first experiment rats were tested for the acquisition of a lever-pressing response reinforced by intravenous heroin injections. This drug was selected because the initial reports showing an effect of housing conditions were based on opiate self-administration and because other lines of evidence suggest that endogenous opioid peptides may be involved in separation distress. In the second experiment rats were tested for the acquisition of intravenous cocaine self-administration. This compound was selected because it represents a different pharmacological class of drug which also has a high abuse potential.

GENERAL METHOD

Subjects

Experimentally naive, male Long-Evans rats weighing between 275 and 375 g were randomly assigned to one of two housing conditions upon receipt from the animal breeder. The first group was housed in individual stainless steel cages ($18 \times 25 \times 18$ cm) that prevented tactile and visual contact among the rats. This housing condition used commercially available cages and a cage rack that is widely used in this and other laboratories for individually housing rats for various experiments. The second condition consisted of rats housed in groups of 10 in a large stainless steel cage ($45 \times 101 \times 39$ cm) that permitted social contact; these rats displayed normal play behavior, dominance struggles, and social grooming. A 12-hour light/12-hour dark cycle of illumination was maintained throughout the experiment, and all behavioral testing occurred during the light phase of this cycle. Prior to arrival in the laboratory, all rats were housed in a grouped condition by the animal breeder (Charles River Breeding Laboratories, Inc., Wilmington, MA). All male groups of 25 rats were housed in a $61 \times 61 \times 23$ cm cage. Subjects ranged from 63 to 91 days old upon arrival in the laboratory.

After the rats had adapted for 1 week to their respective laboratory housing conditions, they were food deprived and trained to lever press for food in an operant chamber using an autoshaping procedure. This procedure requires 3 to 4 days of training, and all rats emitted lever-press rates exceeding 45 responses per hour by the end of this training. The rats had free access to food and water in their home cages throughout the remainder of the experiment.

Surgery

About one week after lever-training, the rats were anesthetized with sodium pentobarbital (60 mg/kg, IP with atropine sulfate, 0.12 mg/kg, SC) and received chronically indwelling intravenous catheters. An autoclaved Silastic catheter (Dow Medical Grade Tubing; outside diameter, 1.2 mm) was inserted into the right external jugular vein and passed subcutaneously to a small incision at the back of the neck. The catheter was connected to a curved 22-gauge stainless steel tube attached to the animal's skull with dental acrylic anchored by stainless steel screws. The stainless steel tube provided a convenient connection for the intravenous infusion line during self-administration testing. Penicillin G procain (60,000 units, IM) was administered prophylactically following surgery.

Procedure

Following a minimum of 10 days recovery from the surgical procedure, the rats were tested for intravenous drug self-administration. Tests were conducted for 2 hours per day, 5 days per week with 2 days of no testing intervening between each 5-day block of testing. A total of 25 2-hour test sessions were conducted over 5 weeks. Individual rats were placed in a $25 \times 25 \times 25$-cm operant chamber containing a single lever. The intravenous catheter was connected to a 20-ml syringe by polyethylene tubing and a fluid swivel (7) which permitted unrestricted movement of the subject during testing. Each lever press activated a motor-driven syringe pump that delivered a 0.25 ml injection over 28 seconds. Lever pressing during the injection interval did not produce a second injection, but lever pressing immediately after completion of the injection interval produced another drug injection. A single daily priming injection was given if the rat did not self-administer drug within the first 10 minutes of testing. Animals were returned to their respective housing conditions (either isolated or grouped) after completion of each 2-hour self-administration session.

Drugs (heroin hydrochloride or cocaine hydrochloride) were dissolved in physiological saline containing 0.3% sodium metabisulfite, and the drug solutions were sterilized by filtration. Intravenous catheters were flushed with 0.2 to 0.4 ml of a heparin-penicillin solution following each behavioral test. Each ml of solution contained 0.3 I.U. heparin to prevent blood coagulation in the catheter and 25,000 I.U. Penicillin G to retard infection.

EXPERIMENT I: HEROIN SELF-ADMINISTRATION

Animals were tested for the acquisition of intravenous heroin self-administration (0.1 mg/kg/injection). Twenty-two isolated rats and 17 grouped rats completed the experiment.

Results and Discussion

Animals in both housing conditions learned to self-administer heroin as demonstrated by a significant increase in drug intake across blocks of testing, $F(4,148) = 32.179$, $p<0.001$. Rats housed in the isolated condition, however, showed significantly higher levels of drug intake, $F(1,38) = 8.263$, $p<0.01$ (see Fig. 1); the Group $\times$ Block interaction was not significant, $F(4,148) = 2.073$, $p<0.1$. Rats in the isolated condition increased their hourly drug intake for the first 4 weeks of testing, while animals in the grouped condition continued to increase their hourly drug intake for all 5 weeks of testing. A Tukey's (a) test was used to compare the isolated and grouped means throughout the 5 weeks of testing. No

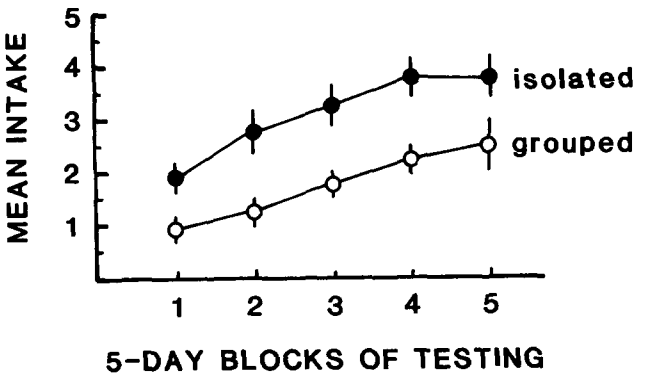

FIG. 1. Acquisition of intravenous heroin self-administration. The figure shows the mean (±SEM) number of injections per hour averaged over 5-day blocks of testing.

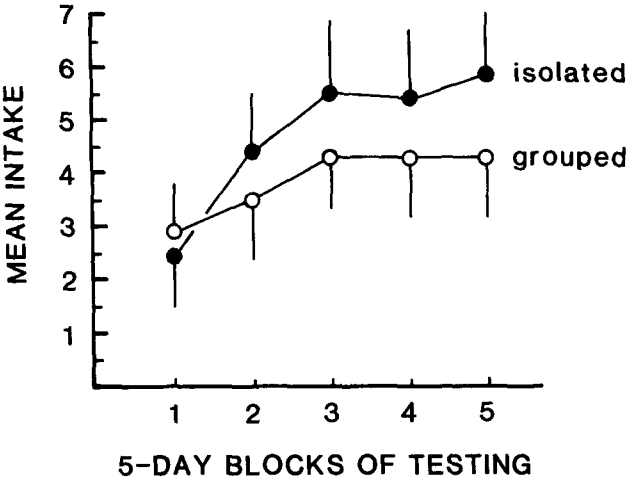

FIG. 2. Acquisition of intravenous cocaine self-administration. The figure shows the mean (±SEM) number of injections per hour averaged over 5-day blocks of testing.

significant difference between the groups was apparent on the first block, while the isolated group self-administered significantly more drug during the second, third, and fourth blocks of testing ($p<0.05$). This difference in drug intake levels was absent on the last block of testing.

The effect of isolation on drug intake appeared to be related to the rate of learning intravenous self-administration. The initial block of testing failed to show a significant difference between groups (despite the obvious fact that the mean intake levels were somewhat different), and the last block of testing revealed that both groups were self-administering similar levels of drug. Only the intermediate blocks of testing showed statistically significant differences in drug self-administration for these two housing conditions.

The assertion that housing influenced the rate of acquisition is supported by examining the percentage of animals learning to self-administer heroin during the first and last blocks of testing. Animals tested for saline self-administration (n = 7) under conditions identical to the isolated group show a mean ± SEM intake of 0.9 ± 0.2 during the first block of testing, yielding a 95% confidence interval of 0.41 to 1.39 responses per hour. During the first block of testing, 63% of the isolated animals and 35% of the grouped animals exceeded saline self-administration levels. By the last block of testing, 91% of the isolated rats and 82% of the grouped rats exceeded the 95% confidence interval of animals tested for saline self-administration.

EXPERIMENT II: COCAINE SELF-ADMINISTRATION

The demonstration that social isolation can influence the level of intravenous heroin self-administration partially supports Alexander's assertion of the importance that housing conditions have on drug-taking behavior and fits well with Panksepp's notion that endogenous opioid peptides are involved in separation distress. Because Alexander studied only opiate drugs and because Panksepp's hypothesis specifically involves endogenous opioid peptides, social isolation would not necessarily be expected to influence the self-administration of other drugs. It is interesting, therefore, to determine if a similar effect on drug-taking behavior will be seen with another pharmacological class of reinforcing drugs.

Two additional groups of rats were treated identically to the first two groups, except that they were tested for the acquisition of intravenous cocaine self-administration (1 mg/kg/injection). Ten isolated rats and 14 grouped rats completed the experiment.

Results and Discussion

Animals housed in the two conditions learned to self-administer cocaine and took similar levels of drug throughout the experiment, $F(1,122) = 0.300$, $p>0.25$ (see Fig. 2). Drug-taking increased slightly across the first weeks of testing and then remained stable, $F(4,88) = 12.640$, $p<0.001$; there was no significant Group × Block interaction, $F(4,88) = 1.787$, $p>0.10$. The percentage of animals exceeding the 95% confidence interval for saline self-administration was the same for the two housing conditions during the first block of testing (i.e., 50%) and was similar for both the grouped and isolated conditions during the last block of testing (64% and 70%, respectively).

Because housing conditions influenced the level of drug intake in the first experiment and because the mean drug intake of the isolated condition was consistently higher than the group-housed condition after the first block of testing, a more detailed examination of the possible effect of these housing conditions is appropriate. Figure 3 shows the group means and the individual drug intake levels for the grouped and isolated rats during the last block of testing. Neither a t-test, $t(22) = 0.906$, $p>0.25$, nor the nonparametric Rank-Sums test ($z = 0.703$, $p>0.48$) revealed a difference between these two groups. This is not surprising when considering the degree of overlap in the two distributions of scores shown in Fig. 3.

The effect of housing condition on the rate of acquiring drug-taking behavior that was apparent with animals learning to self-administer heroin was not seen with animals learning to self-administer cocaine. This finding shows that the influence of housing condition on the acquisition of drug self-administration is not present for all reinforcing drugs and may be specific to opiates.

GENERAL DISCUSSION

Animals in both the isolated and grouped housing conditions learned to intravenously self-administer heroin and cocaine. Social isolation did affect the first weeks of heroin self-administration, but the group-housed animals also learned to self-administer drug, and there were no significant differences in levels of drug intake

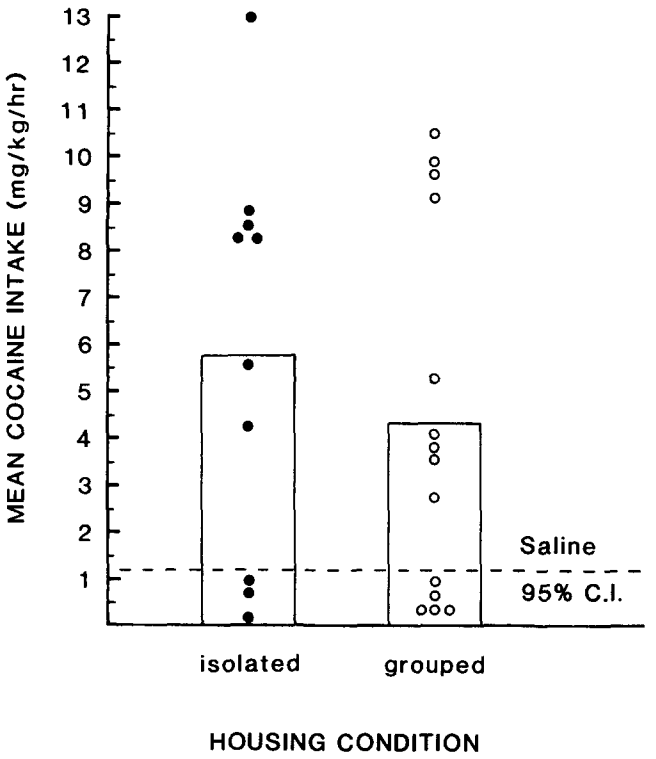

FIG. 3. Drug-intake levels for individual rats self-administering cocaine during the last 5-day block of testing. The group means are indicated by the bars, and the upper limit of the 95% confidence interval (C.I.) for saline self-administration is shown by the dashed line.

by the last week of testing. In this study the effect of housing was limited to an influence on the rate of learning to self-administer heroin, and social housing did not prevent the acquisition of intravenous drug self-administration. This finding clearly shows that social isolation is *not* a necessary condition for opiate reinforcement, although it does appear to influence the initial reinforcing impact of this drug. In contrast, there were no significant differences in cocaine self-administration produced by these two housing conditions throughout the five weeks of testing. This suggests that the effect of housing may be specific to a single class of reinforcing drugs and not important for the self-administration of other compounds.

It might be suggested that the social isolation of the test situation is enough to precipitate drug self-administration that would not occur if the animals were tested in a social situation. Methodological difficulties prevented testing intravenous self-administration in grouped animals. Infusion lines become entangled if several subjects are tested concurrently, and rats housed with even a single subject connected to an infusion line gnaw on the infusion line and physically disrupt drug-taking behavior. However, it is clear from the present study that chronic isolation is not a necessary condition for a drug to be reinforcing. Moreover, it is unlikely that the 2-hour test periods used in this experiment were sufficiently stressing to motivate drug intake. The animals in these experiments were tested during the portion of their light/dark cycle when they are normally asleep, and their social interactions at this time are at a minimum.

The fact that most laboratory animals learn to self-administer intravenous heroin if they are simply given the opportunity has led to the suggestion that all mammals are at risk for opiate addiction. The data from the present experiment are consistent with this view. Although socially isolated animals learned to take heroin more quickly, group-housed animals learned to self-administer drug and showed levels of heroin intake similar to isolated animals by the completion of testing. The fact that grouped animals learned to self-administer heroin somewhat slower than isolated animals suggests that social isolation can influence intravenous heroin self-administration and is consistent with Panksepp's work (10, 11, 13, 14) suggesting that endogenous opioid peptides are involved in separation distress. The fact the group-housed animals did learn to self-administer heroin, however, shows that social isolation is not necessary for heroin to be reinforcing. This is consistent with the view that addictive drugs derive their potent reinforcing actions by pharmacologically activating brain mechanisms involved in motivation and reward and that no special conditions are necessary for this reinforcing action to occur (5, 6, 15, 16).

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