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Housing Conditions Influence Acquisition of Sufentanil Aerosol Self-Administration in Rats

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WEINHOLD, L. L., L. G. SHARPE AND J. H. JAFFE. *Housing conditions influence acquisition of sufentanil aerosol self-administration in rats.* PHARMACOL BIOCHEM BEHAV 44(1) 141–144, 1993.—At weaning, rats were housed either individually or in pairs and as adults were trained to poke their nose in and out of a port that dispensed a 2-s exposure of sufentanil aerosol (50-μg/ml solution). During the acquisition phase, which consisted of five nightly sessions lasting 14–16 h, individually caged rats responded for more sufentanil aerosol than did pair-caged animals when the fixed ratio (FR) requirement was gradually increased from FR 1 to FR 5 over the five sessions. During the maintenance phase, which consisted of daytime 2-h sessions at an FR 5 schedule of reinforcement, there were no differences between individually and pair-caged animals responding for sufentanil or for water vapor. Both groups responded significantly more for sufentanil than for water vapor. Based upon present evidence, it is suggested that environmental and biologic determinants may change psychomotor behavior in a way that could influence the rate by which animals acquire drug-seeking behavior.

Housing conditions Sufentanil aerosol Self-administration Environment

ENVIRONMENTAL determinants appear to alter certain aspects of drug-seeking behavior and have been studied in animal models to gain information about vulnerability to drug abuse. Preexposure to amphetamine (11), cocaine (8), food deprivation (4) and isolate-rearing conditions (13) accelerates the acquisition of self-administration of psychomotor stimulant drugs in rats. However, two studies show different effects of housing conditions on cocaine intake. In one, rats reared in a socially enriched environment and then caged singly for 9–25 days drank more cocaine solution than did isolate-reared rats (5). In another, rats caged individually as adults for 10–35 days acquired IV cocaine self-administration at rates no different from rats housed in groups (2).

Reports vary about differential housing effects on self-administration of opiates, where part of the problem lies in comparing intravenous with oral routes (2). Isolate and grouped rats exposed to water and a morphine solution consume little morphine regardless of the length or beginning of housing condition (1,5). However, when given a complex series of experimental paradigms that include forced consumption of morphine rats caged singly consume more morphine than do group-housed rats (1). Another study showed that rats, after 3 weeks of isolation as adults, acquire a lever-pressing response reinforced by intravenous heroin with rates much faster than animals in a group-housing condition (2). Once responding was stabilized, no differences in self-intake of heroin occurred between the two groups.

A clear distinction as to how such variables might influence the acquisition phase as opposed to a stabilized maintenance phase of drug-seeking behavior is not always apparent. Until recently, most investigators studied aspects of drug self-administration in individually caged animals after the behavior was well established. Acquisition procedures vary considerably among laboratories. Such procedures as food deprivation, preexposure to the reinforcing drug, food-maintained responding, testing during the active cycle, priming, and behavioral shaping procedures have been used to hasten drug self-administration, procedures that may vary among animals. To study the acquisition of drug self-administration requires careful fixed procedures using doses that will differentiate the determinants under investigation (6,12). And, unless the oral route is used grouping animals with intravenous catheters exposed to cage mates adds a practical disadvantage when studying the effects of differential housing conditions on the acquisition of drug-seeking behavior. In the present study, we used a method of self-administration developed in our laboratory in which we found that rats will reliably self-administer sufentanil citrate in aerosol form (8). Unlike the oral route, this inhalation model of drug self-administration has the advantages of the intravenous route in that drugs are quickly absorbed with a rapid onset of action. The obvious advantage over the intravenous route is that no surgery is required for catheterization, animal movements are unrestricted and longer experiments can be conducted in which grouped animals interact with each other without complications related to catheter damage. We report here that rats individually housed since

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weaning for 85 days learned to acquire self-administration of sufentanil vapor during five overnight sessions more rapidly than did animals housed in pairs. No differences between the two groups occurred during 2-h daytime sessions when responding became stabilized.

METHOD

Subjects

Upon arrival, 12 Sprague-Dawley male rats (25 days of age, Charles River, Wilmington, MA) were either housed individually (n = 6) or with a weight-matched cage mate (n = 3 pairs). All rats had free access to food and water throughout the experiment. Lights were on from 0600–1800 h. Rats were weighed before each self-administration session. Standard Plexiglas cages (43 × 20 × 20 cm) were used in both individual and paired-housing conditions.

Apparatus

The operant chambers used for self-administering vaporized solutions was previously described (8). Briefly, the operant chambers (Coulbourn Instruments, Allentown, PA) were sound-attenuating, and the schedule requirements and recording of data was accomplished by interfacing a SKED-11 computer with the chambers through Coulbourn relay circuits.

The vaporized solutions were delivered to the inlet port of the vapor chamber by a commercial nebulizer (model 65 Ultrasonic Nebulizer, Devilbiss Co., Somerset, PA, particle sizes = 0.5–3 μm, according to DeVilbiss specifications). The operant response (nose-poking) activated the nebulizer and within 1 s a cool, fog-like aerosol was propelled into the inlet port of the vapor chamber for 2 s. Time out after each aerosol delivery was 1 min.

Procedure

In our previous study (8), the operant response was lever pressing. In the present study, the operant response was nose-poking into a vapor inlet port located 13 cm above the chamber floor. Approximately 12 weeks after arrival, the acquisition phase of sufentanil aerosol self-administration began. Animals were given access to nose-poke for sufentanil vapor in five nightly sessions (1600–0800 h) lasting from 14–16 h. At least 48 h lapsed between sessions. The nose-poke response was under fixed ratio (FR) requirements, which was systematically increased from 1 to 5 over the 5 days. During the first session, an FR 1 requirement was used for the first 45 min, followed by an FR 2 schedule of reinforcement for the remainder of the session. Subsequent FR increments in night sessions two to five were: FR 2 to 3; FR 3 to 4; FR 4 to 5; and FR 5. Water was continuously available during the sessions.

After the five nightly sessions, animals were shifted to 2-h daytime sessions that occurred between 1300–1600 h. At least 48 h separated the sessions. Daytime sessions continued until responding under an FR 5 schedule for sufentanil vapor became stabilized (less than 20% variation for three consecutive sessions).

For whatever reason, 2 of the 12 rats (1 individually housed and 1 housed with cage mate) failed to meet a previously determined criteria (8) in responding for sufentanil aerosol (an average of one nose-poke/h in nightly sessions). The data from these two rats were eliminated from the study.

The maintenance phase began after stabilized responding had occurred. Rats were exposed to alternating three-session blocks of sufentanil and water vapor. Each session lasted 2 h and was separated by at least 48 h. These series of experiments lasted until five blocks each of sufentanil and water vapor sessions were completed.

Drugs

Sufentanil citrate (generously supplied by Janssen Pharmaceutica, Piscataway, NJ), a highly potent μ-opioid agonist, was dissolved at 50 μg/ml in double-distilled water. This concentration was used because it was the middle dose in the dose–effect curve for self-administration in rats (8).

Data Analysis

Two-way (group × time) and three-way (group × time × treatment) analyses of variance (ANOVAs) with repeated measures over time and treatment were conducted on the number of sufentanil vapor occurrences/h during the acquisition phase and the number of sufentanil and water vapor episodes during the maintenance phase.

RESULTS

Figure 1 shows that over the five nighttime acquisition sessions the individually housed rats self-administered slightly but significantly more sufentanil aerosol than did rats housed with a cage mate, $F(1, 50) = 5.6$, $p < 0.05$. Although responding was nearly identical for the two groups during the first session (FR 1-2), responding during the fifth session (FR 5) by the isolate-reared was about twice that of paired-reared rats (a mean total of 390 vs. 170 nose-pokes, respectively).

When testing was moved to 2-h sessions during daylight hours (Fig. 2), both groups increased their number of sufentanil presentations/h (first three-session block), but the group differences persisted; individually caged animals self-administered about 1.6 times as many sufentanil vapors as paired-caged animals, $F(1, 8) = 9.2$, $p = 0.016$. However, after the fourth of three-session blocks in which sufentanil and water vapor were alternated the two groups were comparable in that both self-administered the same amount of vaporized sufentanil and water with a significant amount of preference for sufentanil over water vapor, $F(1, 99) = 117$, $p < 0.01$.

DISCUSSION

The results of this study indicate that environmental factors such as rearing under differential housing conditions can affect the rate by which adult rats acquire self-administration of opiates, that is, isolate-reared rats acquired self-administration of sufentanil vapor faster than rats reared with a cage mate. However, once sufentanil-maintained responding became stable in both groups this group difference disappeared. Our results support those of Bozarth et al. (2), who found that even though rats that were isolated during maturity learned to acquire heroin self-injections faster than did rats in social groups both groups maintained the same rate of responding during the maintenance phase.

It is reasonable to postulate that all environmental factors that increase the acquisition of drug-seeking behavior do so by increasing locomotor behavior and/or the reinforcing effects of drugs. Upon first exposure, the active animal has more occasions than the inactive one to respond (lever press or nose-poke) to the reinforcing properties of a drug. Indeed, animals selected for their high locomotor activity learn amphetamine self-administration (nose-poke, FR 1) faster than

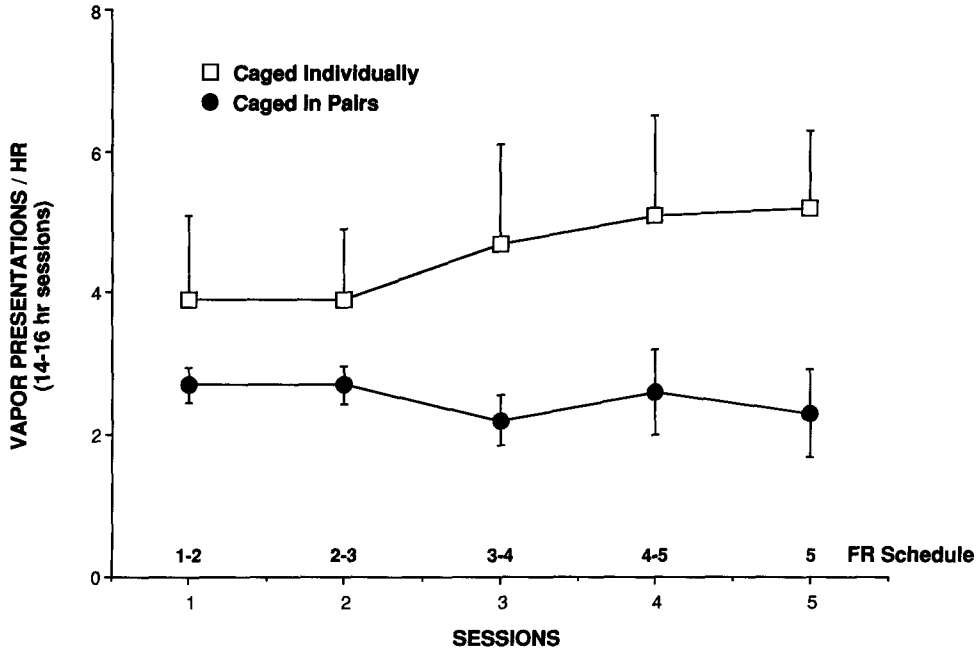

FIG. 1. Acquisition phase of individually housed and pair-housed (85 days since weaning) rats nose-poking for vaporized sufentanil on an fixed ratio (FR) schedule of reinforcement. The FR ratio requirements were increased from FR 1 (session 1) to FR 5 (session 5) in sessions lasting 14–16 h. Sufentanil concentration = 50 μg/ml.

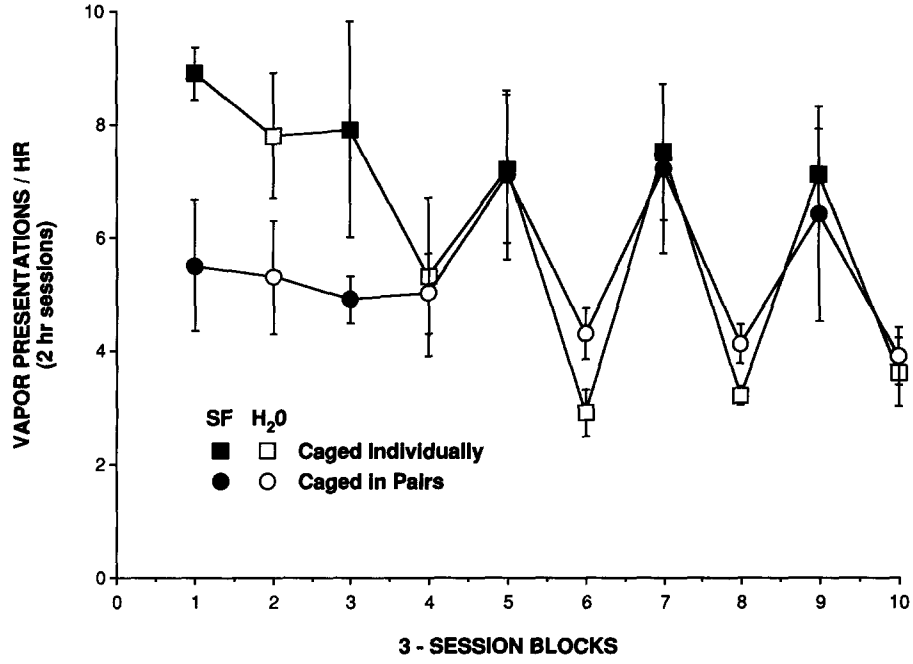

FIG. 2. Effects of housing conditions on the amounts of sufentanil aerosol and water vapor self-administered during the maintenance phase. From the second block of exposures to water vapor (sessions 10–12), both groups self-administered similar amounts of sufentanil aerosol (closed symbols) and similar amounts of water vapor (open symbols). In both groups, significantly more sufentanil was self-administered than water vapor.

less active animals (11). When preexposed to sensitizing doses of amphetamine, less active rats acquire amphetamine self-administration at rates no different from their more active counterparts (11). Evidence that locomotor activity is positively related to acquisition of amphetamine self-administration (12) strengthens the view that behavioral activity per se could account for individual vulnerability to acquire self-administration of a reinforcing drug. Variables that accelerate acquisition of drug-seeking behavior, including isolation at weaning (13), food deprivation (4), and sensitization to psychomotor stimulants (7), have also been shown to increase locomotor activity (3,7,9,14). In addition, it is unknown to what extent these factors are specific to the acquisition of reinforcing drugs.

However, the type of locomotor activity caused by these variables appears to be important. The term "psychomotor" was used to describe forward locomotion in which the rat explores with increased responsiveness to environmental stimuli (15). Mesolimbic dopamine systems appear to mediate this behavior, as well as the rewarding effects of addictive drugs, a coupling of two effects that led to the psychomotor stimulant theory of addiction (15). Therefore, the differential rewarding effects caused by environmental factors cannot be disregarded. For example, food deprivation appears to increase the reinforcing effects of opiates and psychomotor stimulants (3). Interestingly, sons of alcoholics are three to five times more likely to develop alcoholism than sons of nonalcoholics and also show a greater amount of motor activity (10). Therefore, it seems difficult to separate the degree to which locomotor activity and reinforcing drug effects contribute to biologic and environmental factors that influence the acquisition phase of drug-seeking behavior.

One may question how important biologic and environmental determinants are in animal models that test the acquisition of drug-seeking behavior if these variables have little influence on the maintenance phase of drug-maintained behavior as in the present study. Because our method avoids the methodological difficulties intrinsic to intravenous self-administration (2), we were able to test animals for an extended period of time (over 90 days) with no difference between isolate- and pair-reared groups. Under optimal conditions, most laboratory animals learn to self administer drugs of abuse. An important question is do these initial group differences caused by biologic or environmental factors disappear or remain once the drug-maintained responding is stabilized? Even though we observed no differences between groups over a 90-day period, other procedures should be tried such as: rate of extinction, rate of reacquisition, dose-response curves to the self-administered drug, shifts in dose-response curves to antagonists, rate of responding at different fixed-ratio schedules of reinforcement, and progressive ratios. These procedures may be useful in developing animal models for understanding individual differences in drug treatment.

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