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ENVIRONMENTAL INFLUENCES UPON DRUG-INDUCED SUPPRESSION OF OPERANT BEHAVIOR[1]

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ABSTRACT

SPARBER, S. B. AND H. A. TILSON: Environmental influences upon drug-induced suppression of operant behavior. J. Pharmacol. Exp. Ther. 179: 1-9, 1971. Rats were trained to press a lever for food reinforcement and stabilized on a schedule which required 30 lever presses for each pellet. Injection of mescaline hydrochloride (10 mg/kg i.p.) just prior to placement into the operant conditioning chamber resulted in a disruption of lever pressing beginning 10 minutes later and lasting about 25 minutes. Removal of the rats from the chamber 2 minutes after the onset of drug action and replacement after 2.5 or 5.0 minutes resulted in resumption of bar pressing almost immediately. Leaving the animals in their home cages for 10 minutes after the injection (latency to onset of action) also resulted in attenuation of the disruptive effects of the drug. Manipulating the dose of mescaline hydrochloride and an examination of *d*-lysergic acid diethylamide interacting with this phenomenon indicated that the attenuation produced by the manipulation appears to conform to log dose-response relationships and that the behavioral effects of at least one other psychoactive drug can be shortened by the manipulation. The implications of these results are 2-fold: 1) The experimental procedure of injecting a drug and looking for behavioral effects at some predetermined time after administration of the drug should take into account environmental factors as mundane as when the animal is placed into the behavioral chamber. 2) The results described for rats may be analogous to the drug-setting interaction commonly reported for humans reacting to psychoactive agents.

In their concise review on the determinants of the specificity of behavioral effects of drugs, Kellcher and Morse (1968) state that "... attempts to hold environmental determinants constant in physiological and pharmacological experiments have obscured the profound effects of environmental factors in modifying the actions of drugs." However, when one examines the literature for drug-environmental interactions, he is hard-pressed to find other than toxicity effects of environmental stressors such as crowding (Chance, 1946), electric shock (Gunn and Gurd, 1940), cage size (Chance, 1947) and elevated environmental temperature (Hohn and Lasagna, 1960). In studies involving self-administration of drugs, manipulation of environmental conditions have also been shown to affect behavior. Clearly, an effective method employed for initiating and maintaining self-administration of depressant compounds (all of which happen to produce physical dependence) revolves about the introduction of one or another form of stressor. Included in this list are conflict contingencies (Masserman and Yum, 1946), shock avoidance schedules (Clark and Polish, 1960; Mello and Mendelson, 1966) and unavoidable, intermittent foot shock (Davis and Miller, 1963). Recently, Thompson and Ostlund (1965) described the importance of environmental influences upon extinction of oral self-administration of morphine solutions by physically dependent rats.

Operant conditioning methods are being used more often to assess behavioral effects of psychotomimetic agents and tolerance to them (Appel and Freedman, 1965, 1968; Tilson and Sparber, 1970). An analysis of dose-response relationships between mescaline and behavioral tolerance to it was under way when we happened upon a phenomenon which we will call

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environment-induced attenuation of behavioral effects of the drug. A rat was given a moderately high dose of mescaline HCl (15 mg/kg i.p.) prior to being placed within an operant conditioning chamber in which he was trained to bar press for food on a fixed-ratio (FR) schedule of reinforcement. Shortly after initiating bar pressing, there was an abrupt cessation of responding which lasted beyond the 42-minute session, so the animal was removed from the operant chamber before resuming bar pressing. Because of the similarity of structure between mescaline and amphetamine, it occurred to us that this prolonged behavioral disruption might be due to some anorexic property of mescaline rather than some other central or peripheral effect. To test this possibility, we presented the rat with a pellet of food which he rapidly ate. From this response, we assumed the rat was capable of eating when presented with food, but when confronted with the contingency of the FR schedule, the drug effects were still operating. To see what the duration of action of this dose of mescaline was, we placed the rat back in the Skinner box and left him there until responding resumed. To our surprise, the rat immediately resumed responding as though replacement into the box acted as a discriminative stimulus which evoked responding prematurely. We have subsequently studied this phenomenon systematically by manipulating time between cessation of responding due to drug administration, withdrawal from the operant chamber and reinstallation of the animal into the operant chamber. An additional experiment examining dose-response relationships and the generality of the phenomenon with another psychoactive compound has been carried out. Manipulations produced dramatic effects and we report these effects in this communication.

EXPERIMENT I. ATTENUATION OF MESCALINE INDUCED BEHAVIORAL SUPPRESSION. METHODS. *Subjects.* Subjects were four male Sprague-Dawley (Simonsen Laboratories, White Bear Lake, Minn.) albino rats, approximately 325 to 375 g. All subjects were individually housed in air-conditioned quarters at 25°C and 50% humidity under day-night rhythm (6:45 A.M. to 6:45 P.M.). The animals were maintained on a 23-hour food deprivation schedule at 70 to 80% free-feeding body weight for the duration of the experiment. Water was available in their home cages *ad libitum*.

Apparatus. The experiment was run in a standard operant conditioning box (Foringer, Rockville, Md.) containing two response levers one of which was nonfunctional. External sound and light attenuation were provided by enclosing the box in an insulated and ventilated outer chamber equipped with a masking noise generator. Programing and recording of schedule events and responses were automatically done with electromechanical equipment.

Rats were trained to bar press for Noyes food pellets (45 mg) on a FR schedule of reinforcement. After stable base-line responding by each animal on a FR 30 (*i.e.*, press the lever 30 times for each food pellet), drug sessions began. The length of each session was approximately 40 minutes.

Procedure. Animals were administered 0.5 ml of isotonic NaCl i.p. immediately before the 40-minute session (saline-control). The following day, 10 mg of mescaline hydrochloride per kg, dissolved in 0.5 ml of saline, were administered i.p. before the start of the session (drug-control). This dose was used because previous studies have shown that FR responding is consistently disrupted within a short period of time after injection and resumes within 40 minutes (Appel and Freedman, 1968; Tilson and Sparber, 1971). Latencies between injection of the drug to onset of the drug's behavioral effect, which was defined as no reinforcement received for a period of two minutes, were determined. Resumption of FR responding was defined as the point in time when the animal received five food pellets. Forty-eight hours later, the above procedure was repeated. The second drug session was separated by 72 hours from the previous one in order to prevent possible tolerance effects (Freedman *et al.*, 1958). In this drug session, the rats were removed from the operant conditioning box and placed in their home cage after a two-minute period in which no reinforcers were obtained. After five minutes they were replaced in the chamber. Latencies between time of injection to the onset of behavioral effects (two minutes without reinforcement) and to the resumption of responding (five pellets) were again noted. Forty-eight hours later, the entire sequence (including both saline- and drug-control sessions) was again repeated, only this time the period in their home cages was shortened to 2.5 minutes, making the total period between last food pellet and replacement in the chamber 4.5 minutes instead of 7.0 minutes as in the previous "home cage" session.

To determine the effects of delaying placement of the rats in the operant chamber after drug injection, the following experiment was performed. Ten milligrams of mescaline hydrochloride per kg were administered i.p. immediately before a session, and the animal was placed into the chamber. This is the same procedure used in the previous

experiments and likewise acted as a drug-control session. Forty-eight hours later a saline-control session was performed, followed the next day by a drug session in which placement into the chamber was delayed. The duration of delay was equal to the mean of the latencies, for each rat, to behavioral disruption (two minutes without reinforcement) from the five previous drug sessions. In addition to studying the effects of delayed placement, this experiment controlled for much of the handling resulting from taking the rat out of and putting it back into the operant chamber in the previous experiments. This entire procedure is presented in abbreviated form in table 1.

TABLE 1

Experimental design: experiment 1

Session[a]	Drug	Experimental Manipulation[b]
1	Saline	A
2	Mescaline	A
3	Saline	A
4	Mescaline	B (5 min)
5	Saline	A
6	Mescaline	A
7	Saline	A
8	Mescaline	B (2.5 min)
9	Saline	A
10	Mescaline	A
11	Saline	A
12	Mescaline	C

[a] Drug sessions were separated by 72 hours.

[b] A, injected and put immediately into behavioral chamber; B, placed into home cage for specified period of time after two minutes of behavioral disruption; C, injected and left in home cage for a period of time equal to the time required for onset of drug's action (see table 2) prior to being placed into behavioral chamber.

RESULTS. Of the six NaCl control sessions that each of the four subjects had, not one session contained a period of no reinforcement (two minutes) which would define it as a behavioral effect. Figure 1 shows the control cumulative records of each rat that contained the longest pause in responding seen in control sessions. In addition, of the four subjects, only one animal, A-19, showed this pause (1.6 minutes) at the early part of the session, as opposed to the other animals which showed slight pausing in the last half of the session. The later pauses are also shaped differently, looking more like post-reinforcement pauses, typical of satiation effects (Ferster and Skinner, 1957).

Table 2 presents the latencies to onset of behavioral action derived from each experimental manipulation in which the animals were placed immediately into the conditioning chamber after drug administration. It is presented in the order in which it was carried out chronologically, with saline control sessions omitted because of the lack of injection effects upon this behavior. The durations of behavioral disruption for the three drug-control sessions (left in chamber for entire session after drug administration) are presented in table 3. One of the most salient aspects of the data is the intra-animal and inter-animal reliability of drug effects, showing a lack of tolerance, for both measures, from session to session. As represented in figure 2, all rats started to respond within 1.5 to 2.0 minutes after being replaced in the chamber subsequent to removal after onset of drug action. This was the case regardless of whether they were removed for 5.0 minutes or for 2.5 minutes. The cumulative records from the sessions in which the subjects were left in their home cages for a period of time equal to their individual mean latencies for onset of action (table 2) are in figure 3. Only rat A-17 showed some semblance of drug action, taking 9.5 minutes before starting to respond and 11.5 minutes for it to receive five reinforcers. This is in contrast to a mean duration of action of 28.2 minutes when left in the chamber after drug administration (table 3). The other three rats started to respond almost immediately, receiving five reinforcers within three minutes.

EXPERIMENT II. DOSE-RESPONSE RELATIONSHIPS AND GENERALITY TO ANOTHER PSYCHOACTIVE COMPOUND. METHODS. In a follow-up experiment, two groups of four rats each were injected with varying doses of either mescaline hydrochloride or *d*-lysergic acid diethylamide (*d*-LSD) and put directly into the operant chamber. Seventy-two hours later the same dose of drug was injected but the rats were kept in their home cages for 10 minutes (all doses) or 30 minutes (highest dose of each drug) prior to placement into the operant chamber. After an additional 72 hours a second drug-control session was repeated to determine if tolerance had developed. A saline-control session was performed on the day prior to each drug session. Most sessions were 60 minutes long, except an additional 10 minutes was allowed if the rat had not received five food pellets at the end of 60

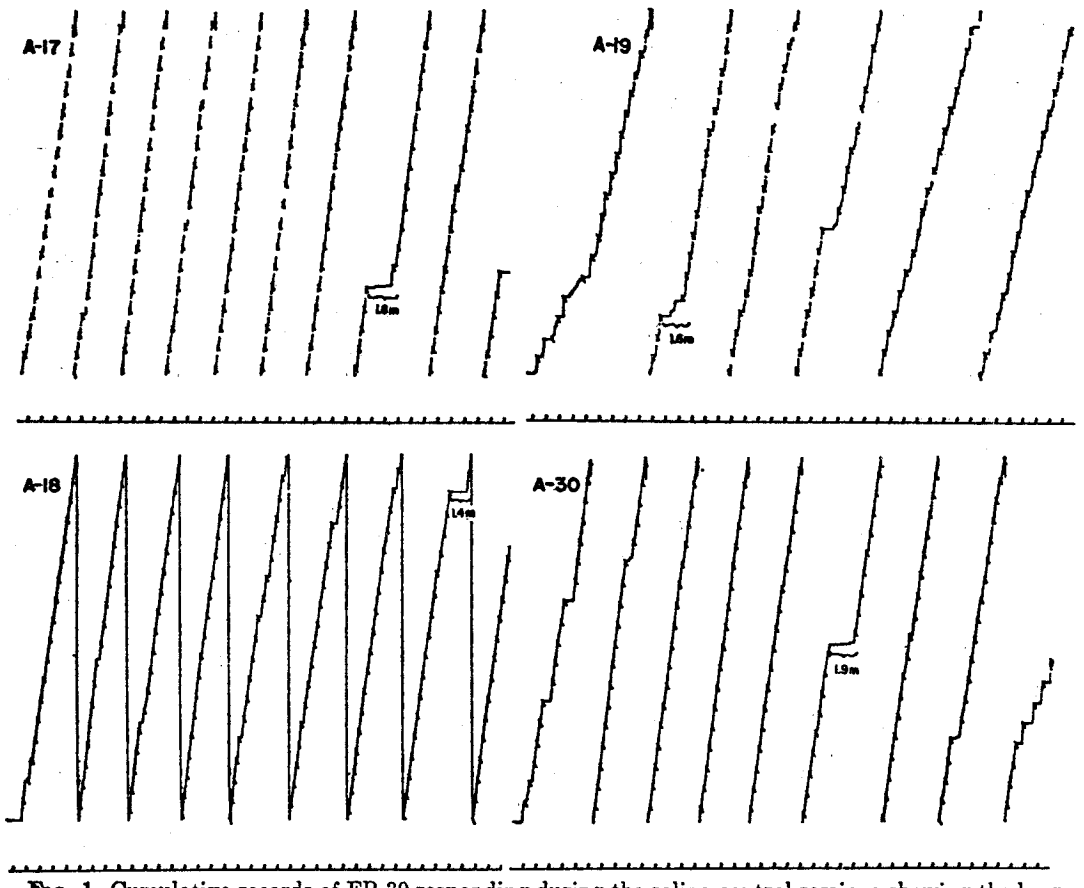

FIG. 1. Cumulative records of FR 30 responding during the saline-control sessions showing the longest pauses without food reinforcement for each rat in experiment I. Pauses ranged from 1.4 to 1.9 minutes and only rat A-19 paused during the first half of the session; the other pauses occurred in the second half of the session and were shaped more like satiation-type pauses. The event marks beneath the cumulative records are a 1-minute time base.

TABLE 2

Latency to onset of behavioral action of 10 mg of mescaline hydrochloride per kg i.p.[a]

Rat	Latency to Behavioral Disruption in Drug Session:					
	1	2	3	4	5	Mean
	min					
A-17	7.0	9.0	8.5	8.5	7.0	8.2
A-18	8.5	12.0	10.5	12.0	13.0	11.2
A-19	11.5	12.0	10.5	6.0	14.0	10.8
A-30	12.0	7.0	10.0	8.5	7.0	8.9
Mean ± S.E.						9.8 ± 0.7

[a] Rats were injected with drug and placed immediately into the operant conditioning chamber. Latency is defined as the period between injection and the point in time where no reinforcers were received for at least two minutes.

minutes. If at the end of this additional 10-minute period the animal still had not responded, the session was terminated and the duration of drug action was based upon the length of the session.

RESULTS. As would be expected, the onset of drug action (two minutes without reinforcement) appears to be inversely related to the dose of either *d*-LSD or mescaline HCl (table 4). In addition, the duration of drug action (time of injection to time of the fifth reinforcer after responding is re-established, minus 10 minutes) conforms to log-linear relationships, except that it is directly related to dose (fig. 4). Since the higher doses of mescaline (15 and 20 mg/kg) resulted in a protracted behavioral disruption, beyond 70 minutes in several instances during drug-control sessions, we see a ceiling effect because of our cutoff period. The effect of keeping the subjects in their home cages for 10 minutes

TABLE 3

Duration of action of mescaline hydrochloride (10 mg/kg i.p.) injected immediately prior to being placed in the operant chamber

Rat	Fifth Reinforcement Minus Latency to Onset of Action in Drug Session:			
	1	2	3	Mean
	min			
A-17	27.0	25.0	32.5	28.2
A-18	24.0	20.5	26.5	23.7
A-19	28.5	20.0	27.0	25.2
A-30	27.0	25.5	21.5	24.7
Mean ± S.E.				25.5 ± 1.0

prior to being placed in the chamber produced a downward shift for all doses of both drugs, resulting in approximately one-third of the duration of drug action when compared to drug-control sessions (fig. 4). Still, the dramatic nature of this phenomenon is not as readily apparent when expressed in graphic form since 10 minutes is the maximum time to onset of action, with the highest dose of *d*-LSD taking an average of only 3.7 minutes to behavioral disruption, even though 10 minutes were subtracted from all values. The possibility that one might design an experiment to show either total disruption of behavior or no effect at all is supported in figures 5 and 6 and table 5. From the data in the figures and table it is obvious that this could be accomplished by merely keeping the animal in its home cage, prior to placement into the experimental chamber, for a period equal to one-half the duration of behavioral disruption seen upon placement immediately after drug administration. For example, animals injected with 0.4 mg of *d*-LSD per kg or 20 mg of mescaline per kg stop bar pressing for 50 to 60 minutes under drug-control conditions but when left in their home cages for 30 minutes prior to placement into the operant chamber respond almost immediately, identical to what was seen in the first experiment for three out of four subjects given 10 mg of mescaline per kg with a 10-minute home cage manipulation. With the low dose of mescaline it was coincidental that the period for onset of action was approximately equal to one-half its duration of action so that we initially chose the wrong parameter (onset to behavioral disruption instead of one-half the duration of action), as a guideline, but nevertheless, got the hypothesized effect.

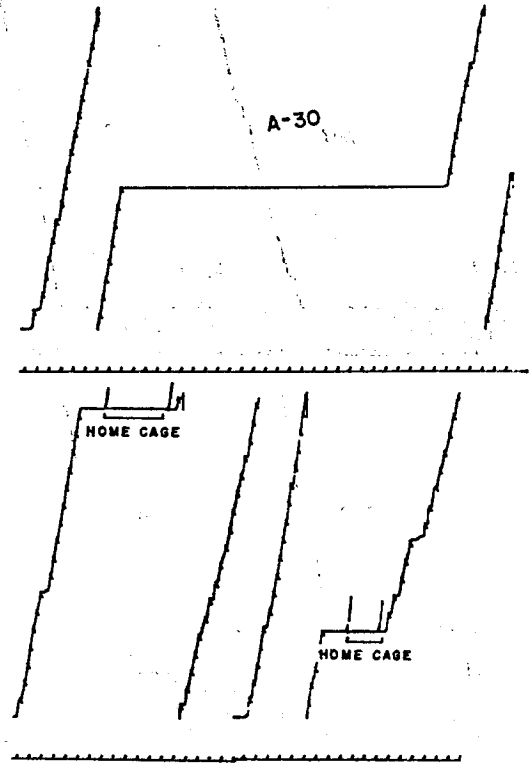

FIG. 2. Cumulative records for rat A-30 showing the behavioral disruption produced by injecting 10 mg of mescaline HCl (i.p.) per kg immediately prior to placement into the operant chamber. Upper record shows the median duration of action of three sessions in which the rat was left in the chamber. The lower records show the attenuation of the disruptive effects by placement of the rat into its home cage for 5 and 2.5 minutes, respectively, after a 2-minute period of no reinforcement. Schedule and time base are the same as in figure 1.

The possibility that the effect was due to tolerance was not supported by any of the data from both experiments. As can be seen in figures 5 and 6, both onset and duration of drug action were the same for drug-control sessions before and after the home cage manipulation sessions.

DISCUSSION. We have seen that 10 mg of mescaline hydrochloride per kg can reliably disrupt an ongoing operant when injected prior to placement within the behavioral chamber. If we remove the animals after 2 minutes of the onset of this behavioral action and replace them in 2.5 or 5.0 minutes, there is essentially complete attenuation of the remainder of behavioral disruption. The possibility that increased handling re-

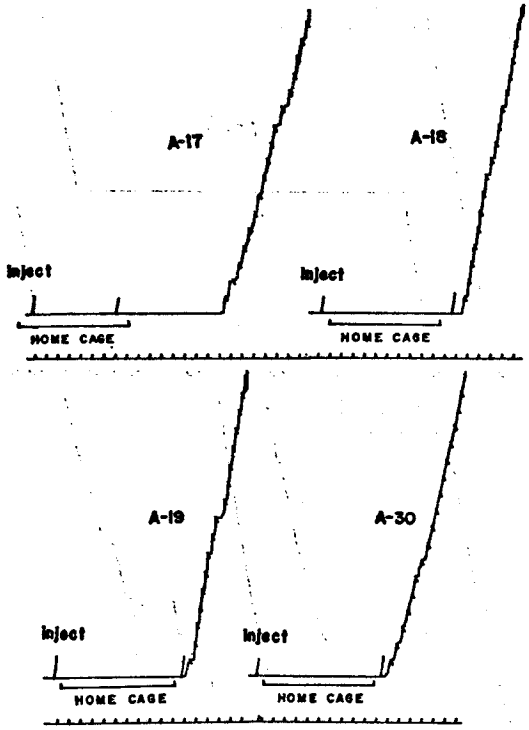

FIG. 3. Cumulative records showing the attenuation of mescaline effects by delaying placement of the rats into the operant chamber for a period of time equal to the mean latency to onset of action (table 1) for each animal. Rat A-17 showed a 60% attenuation compared to the sessions in which no manipulation was carried out. The other three rats showed virtually 100% attenuation of the behavioral disruption caused by 10 mg/kg of mescaline HCl. Schedule and time base are the same as in figure 1.

TABLE 4

Latency to onset of behavioral action of mescaline hydrochloride and d-LSD[a]

Drug Dose	Time to Behavioral Disruption
mg/kg	*min* ± *S.E.*
d-LSD	
0.15	5.4 ± 0.5
0.20	5.1 ± 0.4
0.40	3.7 ± 0.5
Mescaline HCl	
10.0[b]	9.8 ± 0.7
15.0	8.4 ± 2.4
20.0	5.7 ± 1.7

[a] Four animals were used for each drug. See footnote in table 2 for definition of latency to onset of behavioral action.

[b] Data derived from animals in experiment I (see table 2).

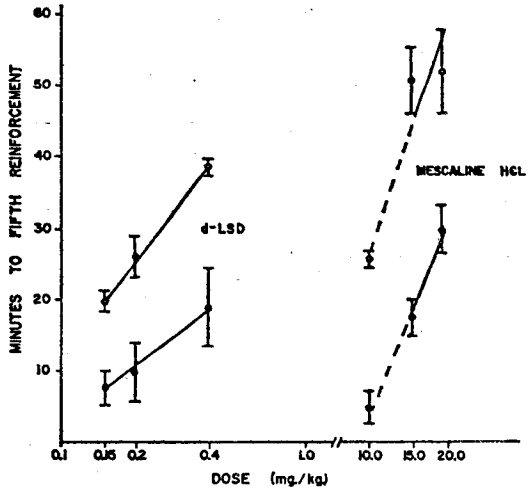

FIG. 4. Duration of action of mescaline HCl and *d*-LSD when injected i.p. with the animals being placed immediately into the operant chamber (○) or after remaining in their home cages for 10 minutes after drug administration (●). In order to compare the two manipulations, 10 minutes were subtracted from the time of injection to resumption of bar pressing (5 food pellets) in the group placed immediately into the operant chamber. Data for the low dose of mescaline HCl is derived from experiment I. Each point represents the mean and vertical lines the S.E.M. of one session each (●) and two sessions each (○) for four animals.

TABLE 5

Effects of home cage manipulation upon the duration of drug-induced behavioral suppression

Drug Dose	Time Spent in Home Cage[a]	Duration of Behavioral Suppression[b]
	min	*min*
Mescaline HCl (20 mg/kg i.p.)	0	61.6 ± 6.0
	10	29.6 ± 3.3
	30	2.9 ± 0.3
d-LSD-25 (0.4 mg/kg i.p.)	0	48.3 ± 1.2
	10	18.9 ± 5.5
	30	1.5 ± 0.2

[a] Rats were injected and placed immediately into the operant chamber or injected and left in their home cages for the specified period of time prior to placement into the chamber.

[b] Mean ± S.E. for four animals in each drug group. Duration in this case refers to the time between injection and resumption of behavior (five reinforcers minus the time spent in their home cages). The onset to behavioral disruption (two minutes without reinforcement) when placed immediately into the operant chamber was 3.7 ± 0.5 and 5.7 ± 1.7 minutes (mean ± S.E.) for *d*-LSD and mescaline HCl, respectively.

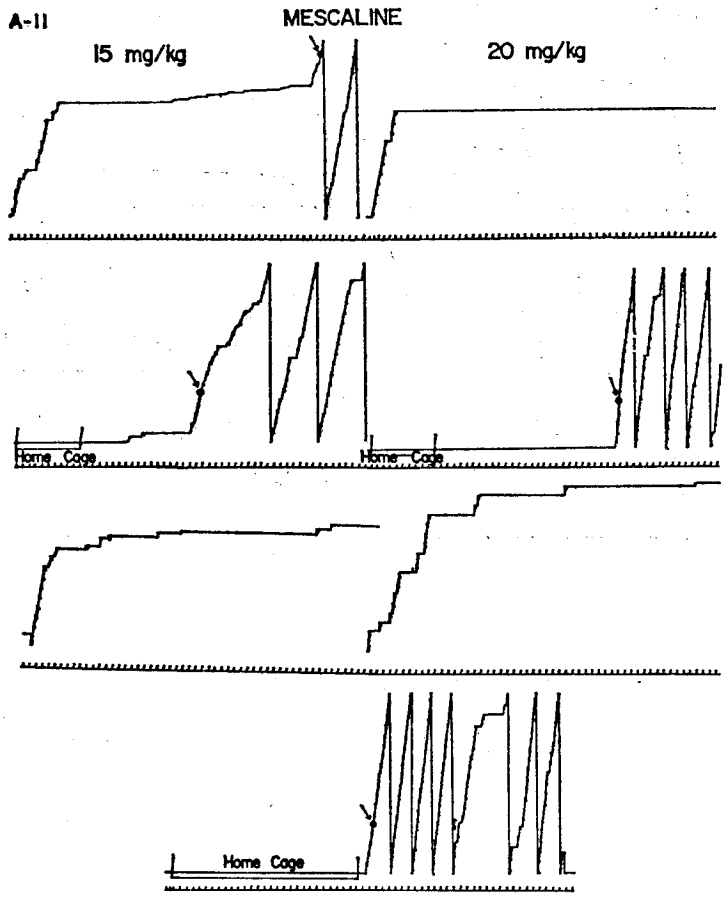

FIG. 5. Cumulative records generated by rat A-11 given 15 and 20 mg of mescaline HCl per kg immediately prior to placement into the operant chamber (top and third from top) or left in its home cage for 10 minutes after injection of both doses (second from top) or for 30 minutes after injection of 20 mg of mescaline HCl per kg (bottom record). Drug administrations were 72 hours apart and lack of tolerance development is demonstrated by equally protracted periods of no bar pressing in sessions before and after the 10-minute home cage manipulation. Circles surround the fifth reinforcement pip when responding resumed before the end of the session. Schedule and time base are the same as in figure 1.

sulting from removal and replacement is the causative variable, acting as a disruptive stimulus during drug action, is argued against by the fact that these animals have repeatedly been handled and injected, with either drug or saline, and habituation should have taken place prior to the procedure that entailed removal and replacement. If, on the other hand, mescaline produced a sensitization to increased handling which in turn obviated the behavioral disruptive effects of the drug, injecting them and delaying their placement in the chamber decreased their exposure to handling and therefore should have at least reversed the attenuation somewhat. This was not the case, since three out of four rats started to respond immediately and the fourth animal showed only a 40% drug effect compared to drug-control sessions.

However, if one assumes that removal of the animal from its cage and carrying and inserting it into the operant chamber acts as a discriminative stimulus complex for initiating bar pressing behavior, which is then followed by reinforcement, the previous arguments against handling and central stimulation (sensitization by mescaline) do not hold up. The observed drug-environment interaction can be interpreted as being a reflection of those stimuli which initiate and perhaps maintain the animal's bar pressing behavior. After drug administration and immediate placement within the chamber, the novel (or aversive) stimulus consequence of drug action

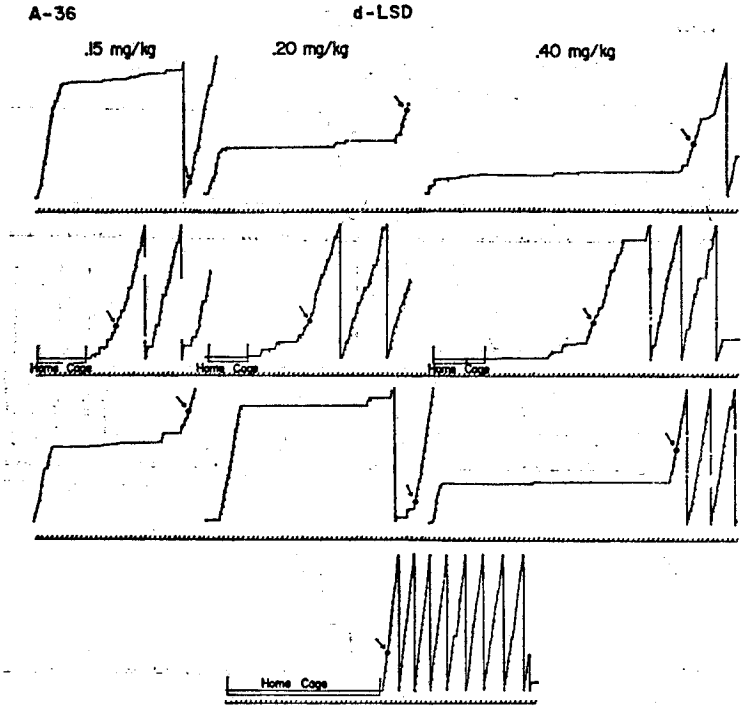

FIG. 6. Cumulative records generated by rat A-36 given three doses of *d*-LSD and placed into the operant chamber immediately (top and third from top) or left in its home cage for 10 minutes after injection of all three doses (second from top) or for 30 minutes after injection of the highest dose (bottom record). Drug administrations were 72 hours apart and lack of tolerance development is demonstrated by equally protracted periods of no bar pressing in sessions before and after 10-minute home cage manipulation. Circles surround the fifth reinforcement pip. Schedule and time base are the same as in figure 1.

disrupts the operant. If maintenance of bar pressing behavior is dependent upon subsequent reinforcement, protracted periods without the reinforcer coupled with the novel stimuli produced by peripheral and/or central action of the drug result in the long duration of action. The stimulus complex of handling, placement into the chamber, etc., appears to be a strong enough initiator of bar pressing to overcome the disruptive effects of the drug. That this is likely is supported by our observation, in a subsequent manipulation, in which an alteration in the stimulus complex of the operant chamber was made. During the 2.5- or 5-minute period after onset of drug action (2 minutes without reinforcement) we introduced a tone and blinking houselight (5/sec) as novel stimuli. This procedure had no attenuating effect upon the duration of drug action.

Recently, Roll (1970) demonstrated the effectiveness of a "reminder" manipulation by replacement of rats upon a bar for self-stimulation after they stopped bar pressing. Although these disulfiram-treated animals were in an altered state of consciousness described as sleep when not bar pressing, replacement on the bar, which presumably resulted in a "free" reinforcing pulse, induced a resumption of self-stimulation. Our animals could not be described as sleeping; they nevertheless seemed to be in an altered state, not engaging in the customary exploratory or grooming behavior when bar pressing is absent or diminished because of satiation or extinction procedures.

Our experiments have pointed out the necessity of considering environmental factors in drug-behavior interaction studies. These environmental factors need not be as severe as overcrowding or increased ambient temperatures which generally tend to interfere with behavior or potentiate drug effects, but can be as mundane as placing the subject in a behavioral testing chamber immediately after drug administration or waiting an arbitrary period of time after

drug administration which in our experiments facilitated the behavior being measured by attenuating the drug effect. For example, observing the behavioral effect of the drug 15 to 30 minutes after administration could result in data showing complete breakdown of behavior or no behavioral effects at all.

That this phenomenon is not a function of a specific drug at a specific dose, but varies in an orderly fashion, is supported by the second experiment with other doses of mescaline and *d*-LSD. The nature of the drug-environment interaction, such as the one described, regarding other schedules of reinforcement and classes of compounds needs further investigation.

CONCLUSION. The psychoactive compounds mescaline and *d*-LSD produce abrupt cessation of fixed-ratio responding by rats followed by periods of no bar pressing, the duration of which is log-linearly related to the dose of drug. By the same i.p. route of administration the latency to onset of behavioral action is inversely related to the dose of drug. Partial or complete attenuation of the behavioral effects of these drugs can be accomplished by leaving the animals in their home cages, after injection, for a period of time equal to one-half the duration of behavioral disruption resulting from immediate placement in the operant chamber. Heightened arousal due to the autonomic and/or hallucinogenic activity of these compounds may result in strengthening the discriminative stimulus (for bar pressing) of placing the animal in the chamber thereby shortening the duration of drug action. The importance of considering this phenomenon in experimental design is obvious. The possibility that this could be used as a model for studying drug-behavior-environment interactions is currently being considered.

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