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DRUG EFFECTS IN SQUIRREL MONKEYS TRAINED ON A MULTIPLE SCHEDULE WITH A PUNISHMENT CONTINGENCY[1]

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The behavior of four monkeys trained on a multiple schedule was differentially sensitive to selected pharmacological agents. The three components of the multiple schedule were: (1) a variable-interval schedule in which responses were reinforced on the average of once per minute; (2) a concurrent schedule in which every tenth response was reinforced and every fifteenth response, on the average, was shocked; and, (3) a neutral stimulus in the presence of which responses were neither reinforced nor shocked. Pentobarbital, chlordiazepoxide, and meprobamate increased responding during each of the components. Scopolamine and d-amphetamine decreased variable-interval performance, had minimal effects on performance during the concurrent-schedule component, and increased responding in the presence of the neutral stimulus. Chlorpromazine decreased variable-interval responding and had slight effects on the responding during the other two components.

Since its introduction by Estes and Skinner in 1941, the conditioned anxiety paradigm has been of continuing interest in the experimental analysis of behavior. This schedule was among the first used to study the effects of reserpine (Brady, 1956*a*, 1956*b*). Variations of it *e.g.*, programming both positive reinforcement and shock punishment cued by a stimulus, are still in use, particularly for the study of compounds which produce barbiturate-meprobamate-chlordiazepoxide-type activity. Recent investigators (Geller and Seifter 1962; Geller, 1962, 1964), using response-contingent shock rather than unavoidable shock (similar to the control schedule used by Brady (1956*b*)), reported that pentobarbital, phenobarbital, emylcamate, hedonal, reserpine, meprobamate, chlordiazepoxide, diazepam, oxazepam, and trimethadione all attenuated the suppression of responding during one component of a multiple schedule when every response was both positively reinforced and punished by electric shock, the other component being a variable-interval schedule. Chlorpromazine, promazine, trifluoperazine, d-amphetamine, benactyzine, and morphine had an opposite effect. The present study employed a multiple schedule similar to Geller's. A non-reinforcement stimulus (S^{Δ}) was added in order to collect information on the role played by stimulus control and to assess the possible value of this component in classifying the pharmacological effects observed.

METHOD

Subjects

Four male squirrel monkeys were maintained in individual living cages on a high fat, high protein diet, with free access to water except during experimental sessions. Each session lasted 4 hr and was preceded by 20 hr of food deprivation; no attempt was made to decrease or to hold body weight constant.

Procedure

A multiple schedule alternated three experimental conditions for 10-min periods. The components were: (1) lever pressing was reinforced by delivering 0.3-cc sweetened condensed milk on the average of once per minute (VI 1-min); (2) every tenth response was reinforced with milk and every fifteenth response, on the average (minimum 2, maximum 60), was shocked (Conc FR 10, VR 15 shock); (3) responses on the lever were neither reinforced nor punished (S^{Δ}). The S^{Δ} condition was correlated with a clicking stimulus Conc FR 10, VR 15 shock by the illumination of a red light; no particular stimulus was corre-

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lated with VI 1-min. A moderate level of illumination was supplied at all times by a small houselight. The secondary reinforcing stimulus was a white light directly above the dipper aperture of the reinforcement device. Feed back after lever responses consisted of a flash from a neon glow-bulb located directly above the lever plus the click produced by the closing of the lever microswitch.

A scrambler delivered nonescapable, 2-sec electric shocks of 2-ma intensity to the grid floor and walls of the chamber during the Conc FR 10, VR 15 shock component.

When performance had stabilized, *i.e.*, no gross changes in response rate per session in each condition for 10 or more sessions, drug tests were begun.

Drugs and dosage schedule

Six compounds were selected: pentobarbital, chlordiazepoxide, meprobamate, scopolamine, d-amphetamine, and chlorpromazine. Single doses (2 cc per kg of body weight) were administered orally 30 min before a 3-hr test session. A single dose was tested each day and every dose of each compound was tested in each monkey. No attempt was made to randomize the sequence of doses. Test sessions were scheduled no oftener than once a week and a control session was usually scheduled the preceding day. (All doses were computed as base weights; pentobarbital was used as the sodium salt, d-amphetamine and chlorpromazine as hydrochlorides, scopolamine as the hydrobromide, and meprobamate and chlordiazepoxide as the base compounds. The compounds were dissolved in water and administered by gavage.)

RESULTS

Figure 1 shows the cumulative records collected during the first hour of two control sessions for one monkey. The schedule conditions indicated by the letters A, B, and C, are shown only for the first 30 min, although the three conditions alternated in the same order throughout the session and the experiment. Minimal responding normally occurred during S^{Δ} (A) when no responses were reinforced, or Conc FR 10, VR 15 shock (B) when every tenth response was reinforced with milk and every fifteenth response, or the average, was shocked. Responding usually started immediately when the VI 1-min component (C) of the schedule was programmed, and was maintained at an even rate until the next stimulus change.

Figure 2 shows cumulative response curves of the performances for the same animal

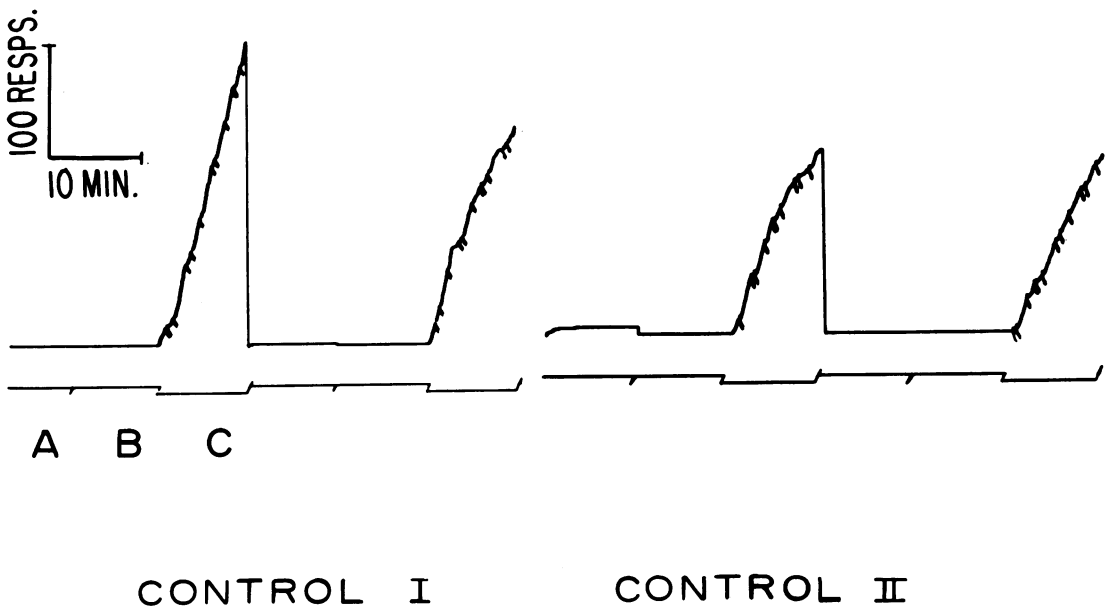

Fig. 1. Cumulative records of multiple-schedule performance generated during the first hour of two control sessions. Each of three components: A = S^{Δ}; B = Conc FR 10, VR 15 shock; C = VI 1-min, alternated for 10-min periods. The VI component is also indicated by the offset of the event-pen.

shown in Fig. 1 during the first hour after the doses were administered which produced the maximal effect on one of the components of the schedule for each of the compounds tested. The sequence of schedule conditions is the same. Responding during the variable-interval component at these doses occurred under all test conditions. Chlordiazepoxide, meprobamate, and pentobarbital increased responding during the VI 1-min component; scopolamine, d-amphetamine, or chlorpromazine did not.

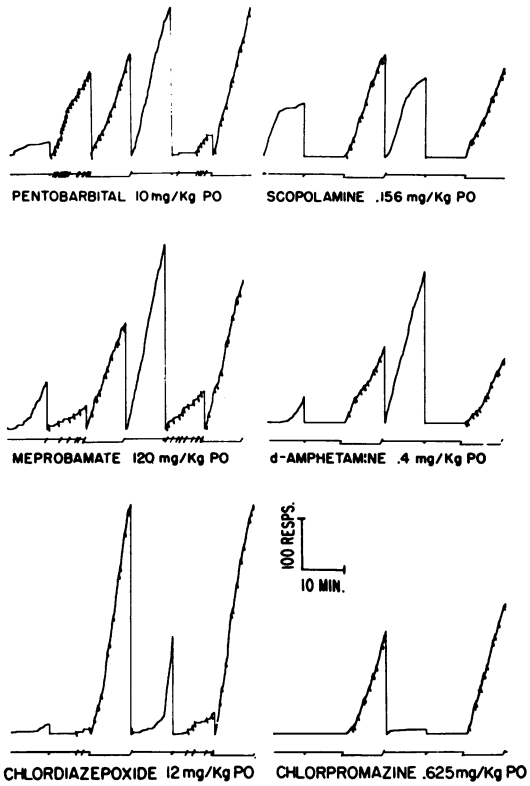

Fig. 2. Cumulative records of schedule performance for the same animal shown in Fig. 1 following dosing with various compounds. The schedule remained the same. Shocks in Conc FR 10, VR 15 shock are indicated by offsets of the event pen.

No increase in responding during Conc FR 10, VR 15 shock was produced by scopolamine, d-amphetamine, or chlorpromazine at the doses tested. However, pentobarbital at 10 mg per kg, meprobamate at 120 mg per kg, and chlordiazepoxide at 12 mg per kg all increased responding during this component; the resultant increase in the number of shocks delivered is indicated in Fig. 2 by "off-sets" of the event pen. All compounds except chlorpromazine increased responding during S^{Δ}.

Figure 3 shows plots of the average data for the four animals. The increased rates of responding during the variable-interval component covered a wide dose range for pentobarbital, meprobamate, and chlordiazepoxide. The other compounds, scopolamine, d-amphetamine and chlorpromazine, systematically reduced responding with increasing doses. During Conc FR 10, VR 15 shock, responding was increased only by meprobamate, pentobarbital, and chlordiazepoxide, the increase in responding being proportional, except for the highest doses of meprobamate and pentobarbital, to the dose administered. Pentobarbital possessed a much steeper dose-response curve than either meprobamate or chlordiazepoxide.

S^{Δ} responding was increased at some doses by all the compounds except chlorpromazine pattern of responding at any dose tested. In Fig. 3, the horizontal lines show the averages of control-level responding for 13 sessions gathered throughout the test period.

The pharmacological activity shown can be summarized as follows: pentobarbital, chlordiazepoxide, and meprobamate produced similar patterns, with increased responding, during all components. Scopolamine and d-amphetamine increased responding during S^{Δ} and decreased responding during variable-interval and during Conc FR 10, VR 15 shock. Chlorpromazine decreased variable-interval responding and even further depressed Conc FR 10, VR 15 shock responding.

DISCUSSION

The data support earlier pharmacological studies which used schedules with response-contingent shock. The data published by Geller and his colleagues showed an increase in variable-interval responding, after meprobamate, chlordiazepoxide, and pentobarbital were administered, comparable to that shown in the present study, although they did not analyze this effect. This moderate increase in appetitively controlled lever pressing remains unexplained, but could possibly be related to the increase in food intake after administration of this class of drugs (Hanson and Stone, 1964). The major changes produced in S^{Δ} performance by those compounds that also modify Conc FR 10, VR 15 shock performance suggest that disruption of stimulus control

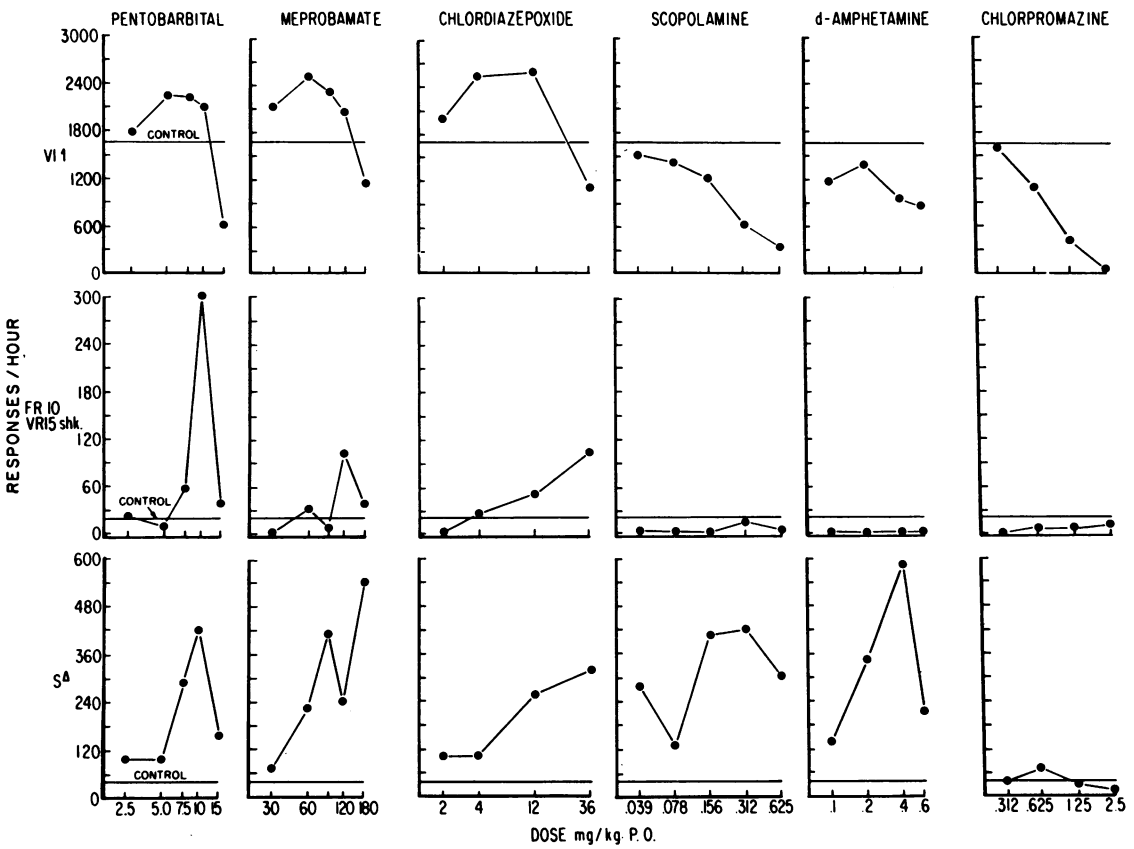

Fig. 3. Average response rates of four animals trained on Mult VI 1-min, Conc FR 10, VR 15 shock, S^{Δ}. Each animal was given each dose of each compound before a 3-hr session.

could be of basic importance in this type of pharmacological activity. Compounds as diverse as scopolamine and d-amphetamine, however, had similar effects on S^{Δ} performance without affecting the schedule component containing the shock contingency. It would appear that the animals were able to discriminate between the various parts of the schedule when administered doses of d-amphetamine and scopolamine; yet control of behavior during S^{Δ} was obviously affected. There is, however, no reason to believe that the two types of activity, *i.e.*, effects on S^{Δ} or Conc FR 10, VR 15 shock, are necessarily a pharmacological entity. This aspect of the behavioral control of the schedule invites further study.

Generally speaking, the drug effects demonstrated in the present experiment, and in those earlier studies which also used response-contingent shock, agree quite well with the drug effects shown in animals trained on a suppression schedule with unavoidable shock.

Lauener (1963), using an approximation of the original Estes-Skinner schedule, reported that five barbiturates, chlordiazepoxide, chloral hydrate, meprobamate, and carisoprodol, were all active in attenuating the conditioned emotional response (CER). Chlorpromazine, ethanol, methylpentanol, methenoxalone, amphetamine, and morphine were inactive. Kinnard (1962) and Ray (1964) were unable to demonstrate the activities of chlorpromazine in reversing the CER. Ray also tested meprobamate and reported that intraperitoneal doses of meprobamate significantly attenuated the CER in half the animals tested. Tamura (1963), working with dogs in a simple lever-pressing situation, showed reversal of shock-suppressed responding with phenobarbital, pentobarbital, thiopental, meprobamate, and ethanol, but was unable to produce reversal with either chlorpromazine or benactyzine. Morse (1964) reported that variable-interval responding in pigeons suppressed by punish-

ment was restored by amobarbital, but not by chlorpromazine.

The similarities in the drug effects reported for the CER and the response-contingent shock situations seem strongly to suggest that identical controls are involved. The method of programming electric shocks in the typical suppression experiment does not specify what behavior is punished; it is highly likely that "superstitious" response-contingent shocks do occur, particularly early in training when variable-interval responding has not yet been suppressed. Further analysis of the contingencies operating at the time of shock delivery in the CER schedule is needed, and would probably help in comparing the behavior generated by these two schedules.

The value of the present schedule for pharmacological studies would appear to be: (1) the inclusion of S^{Δ} offers sensitivity to at least two other pharmacological classes of compounds, and, (2) scheduling the various components of the schedule for equal periods of time offers large segments of the suppressed behavior for study.

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