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Effects of Scopolamine, Amphetamine and Benzodiazepines on Conditioned Suppression[1]

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MICZEK, K. A. *Effects of scopolamine, amphetamine and benzodiazepines on conditioned suppression.* PHARMAC. BIOCHEM. BEHAV. 1(4) 401–411, 1973.–Conditioned suppression of operant behavior was produced by preshock stimuli (i.e., stimuli that precede the noncontigent presentation of electric shock), or prereward stimuli (i.e., stimuli that precede the noncontingent presentation of food) in rats and squirrel monkeys responding on a variable interval schedule of food reinforcement. Benzodiazepine derivatives and amphetamine differentially affect conditioned reactions which are elicited by preshock and prereward stimuli. Conditioned suppression to prereward stimuli were unaffected by chlordiazepoxide, diazepam, scopolamine hydrobromide and scopolamine methyl nitrate but clearly reduced by amphetamine. On the other hand, chlordiazepoxide attenuated the conditioned suppression to preshock stimuli whereas amphetamine, scopolamine hydrobromide and scopolamine methyl nitrate had no significant effects in this paradigm. The results suggest that the effects of drugs on conditioned suppression cannot be interpreted, *a priori*, in terms of selective effects on mechanisms related to emotional behavior or inhibition.

Scopolamine hydrobromide Scopolamine methyl nitrate *d*-Amphetamine Chlordiazepoxide Diazepam

Conditioned suppression Anxiety Inhibition Conditioned responses Rats Squirrel monkeys

WHEN a neutral stimulus (CS) which terminates contiguously with a painful stimulus (US) is repeatedly presented while an animal is engaged in operant behavior such as lever pressing, operant responding comes to be suppressed in the presence of the CS. Since this conditioned suppression [28] was found to correlate with defecation, urination, freezing etc., it has been widely used as an experimental measure of conditioned anxiety [15] or conditioned emotional response (CER) [23]. This procedure has been frequently employed in the evaluation of drugs suspected of a selective action on emotional behavior [10,36].

Several studies report that drugs such as reserpine eliminate conditioned suppression but also depress the baseline rate of operant responding [2, 8, 33]. Stimulants such as amphetamine elevate the baseline operant behavior but do not significantly alter conditioned suppression [8,25]. The benzodiazepine derivatives, on the other hand, have recently been reported to attenuate conditioned suppression without affecting the operant baseline [25, 34, 36]. This selective effect of the benzodiazepine derivatives on the conditioned suppression has been interpreted as support for the contention that these drugs may act specifically on central mechanisms concerned with emotional states [29].

An alternative explanation is suggested by Wuttke and Kelleher's [39] model of benzodiazepine action. According to this view, a reduction of the response suppression in the conditioned suppression paradigm may be due to the fact that benzodiazepine derivatives may increase any low-rate behavior whether it is suppressed by punishment, conditioned suppression or other, nonaversive procedures. Similarly, Margules and Stein [29] suggested that benzodiazepine derivatives may not specifically enhance aversively suppressed behavior but rather increase the general tendency to respond in various situations involving behavioral suppression. They further hypothesized that this facilitation of behavior may be due to a general disinhibition of a central cholinergic system.

That conditioned suppression seems to require active inhibition of ongoing behavior [12] is suggested by findings based on a discrete trial conditioned suppression paradigm, first described by Leaf and Muller [26]. Several studies have shown that anticholinergic drugs eliminate this type of conditioned suppression, and this effect has been attributed to an interference with a central inhibitory cholinergic mechanism [4, 5, 16, 37]. On the other hand, anticholinergic agents were found to have no effect on the response suppression produced by the Estes-Skinner procedure [7, 20].

According to the hypothesis of Margules and Stein [29] anticholinergic drugs and benzodiazepine derivatives should disinhibit responding suppressed by a conditioned suppression paradigm in a similar manner. Two conditioned sup-

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pression procedures were designed which produced stable response suppression to a comparable degree over several months, in order to test the conclusions and predictions of Wuttke and Kelleher's [39] and Margules and Stein's [29] hypotheses on the action of the benzodiazepine derivatives and anticholinergic drugs.

EXPERIMENT 1: CONDITIONED SUPPRESSION DURING A PRESHOCK STIMULUS

An Estes-Skinner-type conditioned suppression procedure was used to compare the effects of scopolamine, chlordiazepoxide and amphetamine. It was the objective to differentiate a drug's effect on baseline behavior and on responding during the conditioned suppression trials on the basis of specific dose–response curves. Miczek [31], for example, found effects with these drugs on punished, punishment-free and extinguished behavior which were differentially dose-dependent.

Method

Animals. Five adult male albino Sprague-Dawley rats were used. During the experiment all rats were maintained at 80% of their free-feeding body weight. Water was available ad lib, except during the experimental session.

Apparatus. An operant test chamber (30.5 x 25.5 x 27.5 cm) (Lehigh Valley Electronics) was housed in a sound-attenuating cubicle. The chamber was equipped with a lever and a white stimulus light (2.5 W) above the lever. A food magazine was connected to a LVE pellet feeder, mounted to the outside of the cubicle. The feeder delivered 45 mg Noyes food pellets. The chamber was illuminated by a 0.3 A 28 VDC light bulb, mounted on the ceiling of the cubicle. Electric current, generated by a 900 VAC source, could be continuously appled to the grid floor with a 47 k resistor and a potentiometer in series. The floor consisted of 0.5 cm dia. stainless steel rods, spaced 1.5 cm apart, and connected by neon light bulbs (NE2). A Sodeco print-out counter was used to record the lever-pressing responses emitted during the presentation of the conditioned stimulus and the equally long control period preceding it. Conventional electromechanical equipment was used for programming and recording the experimental events.

Procedure. The rats were tested at 23 hr after feeding. They were magazine trained and shaped to press a lever, each lever press being reinforced by the presentation of a food pellet. After this training period, lever pressing was reinforced according to a variable interval schedule of reinforcement which had a mean interval between scheduled reinforcements of 30 sec with a distribution of intervals varying from 5–60 sec. (VI 30 sec). Each daily session lasted 40 min.

After responding on the VI 30 sec schedule had stabilized, a white stimulus light was presented for 20 sec at irregular intervals two or three times during each session. After the presentation of the light ceased to affect the response rate, a 0.5 sec duration electric shock (UCS) was delivered contiguous with termination of the light. After about 10 sessions under these conditions all rats suppressed responding during the light (CS). The intensity of the UCS shock was adjusted by manipulating the resistance in series with the grid floor so that the response rate of each rat during the CS was suppressed to 25% or less of the rate during a control period immediately preceding the CS and of the same length as the CS (PRE-CS).

The rate of responding during the CS and the PRE-CS as well as the overall session operant baseline response rates were adopted as indices of stability. A change in the experimental procedure or a drug administration was scheduled only if all three measures of response rate did not vary more than 10% from the overall mean for three successive experimental days.

Drugs. *d*-Amphetamine sulfate, scopolamine hydrobromide, scopolamine methyl nitrate were dissolved in 0.9% saline. Chlordiazepoxide hydrochloride was diluted in sterile water for injection (Lilly No. 208). Tertiary and quaternary scopolamine were administered IP, *d*-amphetamine and chlordiazepoxide were administered IM. Injection volume was always 1 ml/kg, and each injection was followed by at least five drug-free days. The injection sequence of different dosages and drugs followed a Latin-Square design. Aperiodic injections of saline served as the control condition and were found not to significantly alter the response rate. *d*-Amphetamine sulfate was obtained from Smith, Kline and French; chlordiazepoxide was purchased in the commercially available 100 mg ampoules (Librium) from Hoffman-La Roche; scopolamine hydrobromide and scopolamine methyl nitrate were puchased from Sigma Chemical Company.

Data evaluation. Predrug, drug and postdrug data were subjected to repeated measures analysis of variance, and the means were compared by the Newman-Keuls or Duncan methods [38].

For each of the two to three CS-US presentations per session a suppression ratio was calculated as described first by Annau and Kamin [1]. This ratio equals B/A+B, where B represents the number of bar presses during the CS, and A the number of bar presses during the equally long control period immedately preceding the CS. If the CS has no effect on the bar pressing, this ratio equals 0.50. If the CS suppresses bar pressing to half of the control rate, the ratio amounts to 0.33. A ratio of 0.00 indicates complete suppression.

Drug effects on operant baseline response rates were assessed by comparing the average rates of responding per minute maintained by the variable interval schedule of reinforcement during the 40 min daily session under drug and control conditions.

Results

Repeated presentations of the light CS, followed by the delivery of painful electric shock, produced a clear suppression of ongoing operant behavior in all rats. Each rat suppressed its rate of lever pressing during the CS to about 10–15% of that during the PRE-CS control period. Conditioned suppression developed within 10 daily sessions and was maintained over several months.

Conditioned suppression of operant lever pressing remained unaltered after administration of *d*-amphetamine at all dose levels (Fig. 1, left top). The average baseline response rate was not significantly changed by the lowest dose of amphetamine (0.1 mg/kg), although two of the five rats increased their responding about 20%. Higher dose levels of amphetamine significantly decreased the baseline response rate in all animals ($p<0.05$ for 2.0 mg/kg) (Fig. 1, left bottom).

Administration of increasing doses of chlordiazepoxide markedly reduced conditioned suppression; the highest dose (33.3 mg/kg) completely attenuated suppression in all rats (Fig. 1, right top). Chlordiazepoxide also increased the

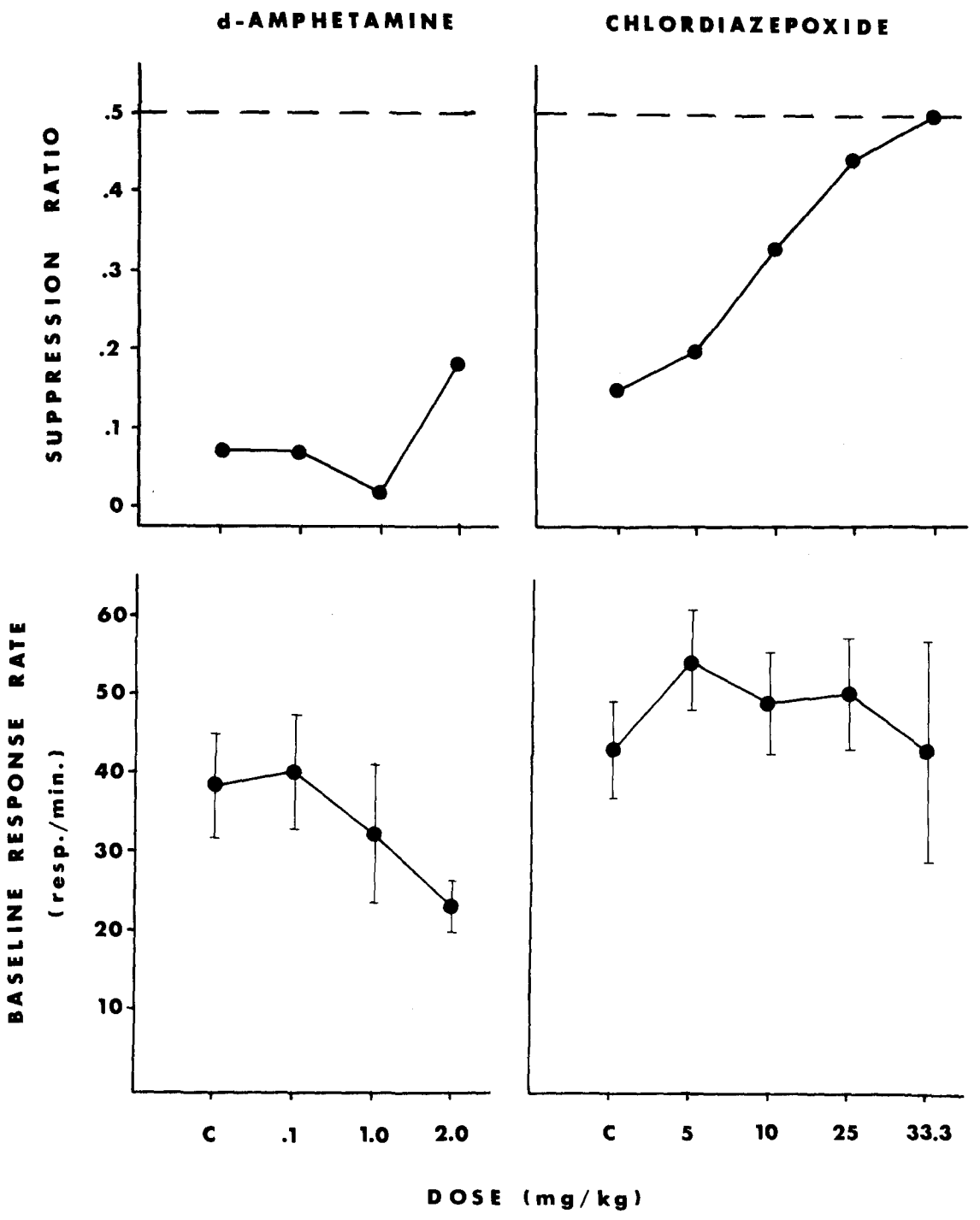

FIG. 1. Effects of *d*-amphetamine and chlordiazepoxide, on the mean suppression ratio during a preshock stimulus (top) and the mean baseline response rate during a VI schedule of reinforcement (bottom) in five rats. The vertical lines in the data points of the baseline response rate graphs (bottom) indicate the range of ± 1 S.E. from the mean rates of responding. "C" refers to the control condition after saline injections.

overall sesion baseline response rates at all dose levels, most effectively at lower doses (Fig. 1, right bottom). In three of the five rats the peak increase in baseline responding was observed at the lowest dose level of chlordiazepoxide (5 mg/kg). The other two rats showed the largest increase in the rate of baseline responding under the influence of 25 mg/kg of chlordiazepoxide. At the 10 mg/kg dose, all five rats showed significant increases in baseline responding ($p<0.05$).

Administration of scopolamine hydrobromide and its quaternary amine derivative did not significantly increase suppressed responding during the CS at any dose level (Fig.

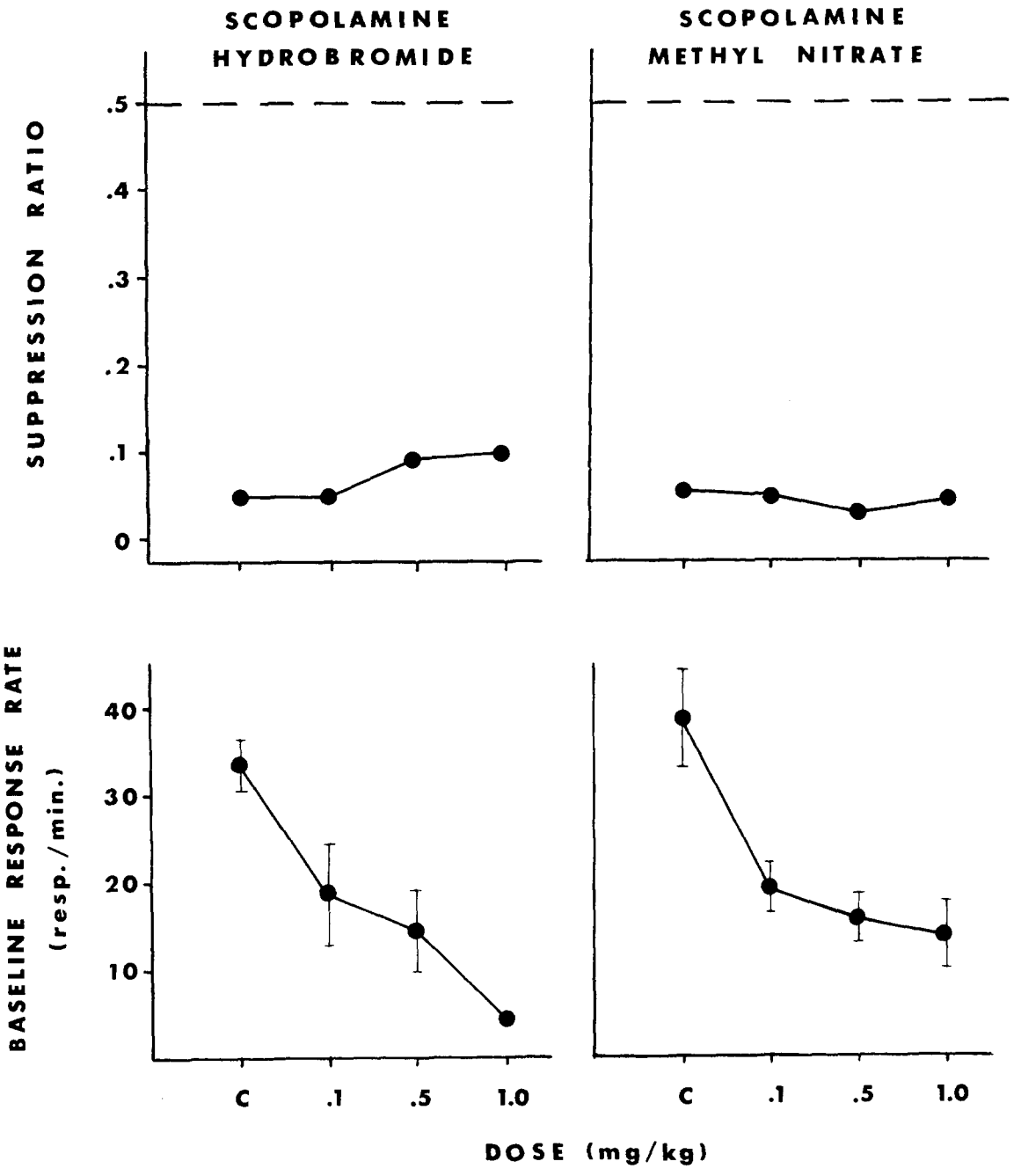

FIG. 2. Effects of scopolamine hydrobromide and scopolamine methyl nitrate, on the mean suppression ratio during a preshock stimulus (top) and the mean baseline response rate during a VI schedule of reinforcement (bottom) in five rats. The vertical lines in the data points of the baseline response rate graphs (bottom) indicate the range of ± 1 S.E. from the mean rates of responding. "C" refers to the control condition after saline injections.

2, top), but significantly decreased baseline responding ($p<0.01$) (Fig. 2, bottom).

Discussion

Scopolamine and amphetamine did not significantly alter conditioned suppression, but reduced baseline responding at higher dose levels. These findings are consistent with previous reports [8, 20, 25] and suggest that well established, stable conditioned suppression in the Estes-Skinner paradigm is not subject to the disinhibitory action of these drugs.

On the other hand, chlordiazepoxide was found to reduce and, at the highest dose (33.3 mg/kg), completely attenuate conditioned suppression. Baseline responding was also enhanced after administration of chlordiazepoxide, but at lower dose levels than those which were most effective to increase the response rate during the CS. These observations

extend those of Lauener [25] in a similar conditioned suppression paradigm and those of Miczek [31] and others (e.g., [17]) in punishment experiments. At higher dose levels chlordiazepoxide increased responding which is suppressed by punishment or by a CS preceding an aversive US more marked and reliable than nonpunished operant behavior. Apparently, chlordiazepoxide's rate-enhancing action on aversively and nonaversively suppressed behavior can be dissociated on the basis of the most effective dose levels in both instances. This supports the hypothesis, proposed earlier [31], that this drug, at higher dose levels (25–40 mg/kg), may have specific effects on processes involved in aversively suppressed behavior. In addition, at lower dose levels, chlordiazepoxide appears to have a general disinhibitory action on nonpunished low-rate behavior, as has been suggested before [29,39]. The more conservative rate-dependency interpretation does not seem to account most parsimoniously for the various behavioral effects of chlordiazepoxide, including attenuation of aversive conditioned suppression, as observed in the present experiment, the punishment-attenuating effect, reported earlier [13,31], the augmentation of time-limited fluid intake [17], as well as the enhancement of operant behavior under various schedules of reinforcement [24].

EXPERIMENT 2: CONDITIONED SUPPRESSION DURING A PREREWARD STIMULUS

Recent behavioral investigations [3, 32] have shown that conditioned suppression can be induced by stimuli that signal the noncontingent presentation of positive reinforcers such as food. The suppression of lever pressing that occurs in this paradigm may represent – in Carlton's [11] framework – an instance of nonaversive inhibition of ongoing operant behavior. This type of behavioral suppression cannot easily be attributed to conditioned anxiety and may thus provide information useful in interpreting the conditioned suppression phenomenon itself. Since response suppression during stimuli which signal the noncontingent presentation of positive reinforcers shows some topographical similarities to the suppression during signals for negative reinforcers, Azrin and Hake [3] have suggested that both procedures may induce a "general emotional state" which leads to the suppression of ongoing operant behavior. If a general emotional state is responsible for both kinds of conditioned suppression, and if the benzodiazepines selectively affect emotional reactions, these drugs should eliminate the response suppression in both paradigms. A similar prediction can be derived from Wuttke and Kelleher's [39] hypothesis that the benzodiazepine derivatives may increase low-rate behavior. Dissimilar drug effects on conditioned suppression to prereward and preshock stimuli, on the other hand, would suggest that different classically conditioned reactions may be responsible for the conditioned suppression of operant behavior in different situations as Miczek and Grossman [32] have suggested.

It is the purpose of the present experiment to compare the effects of chlordiazepoxide, diazepam, scopolamine and amphetamine on conditioned suppression reactions to prereward stimuli.

Method

Animals. Five squirrel monkeys *(Saimiri sciureus)* and eight rats of the Sprague-Dawley strain were used. All rats and monkeys were deprived of food such that they were maintained at 80% of their free-feeding weight. Water was available at all times, except during the experimental sessions.

Apparatus. For the monkeys a restraining chair similar to the one described by Hake and Azrin [19] (LVE Model 1619) was used. During the experimental session the monkey was partially restrained by a waist lock. A metal lever (LVE Model 1352) protruded through a 3.5 cm slot on the left side of the front wall 6 cm above the waist level. A food receptacle was mounted in the center of the front wall which was connected to a Ralph Gerbrands feeder delivering 45 mg Noyes pellets, and to a Foringer feeder, delivering 190 mg Ciba banana pellets. The Noyes pellet feeder was mounted in the back of the front panel and Foringer feeder was mounted outside of the chamber enclosure. On the left sidewall a solid state miniature audible signal generator (Mallory sonalert) was mounted 22 cm above the waist level. The signal device generated a tone of 80 db SPL.

For the rats an operant test chamber was used similar to the one described in Experiment 1. In addition to the lever, food magazine and feeder, a spout for the delivery of liquid reinforcements was mounted next to the food magazine. The spout was connected to a solenoid valve (LVE Model 1527), mounted on the outside of the cubicle. A 100 cc liquid reservoir was connected to the valve. The reservoir was filled with sweetened milk (25% condensed milk, 75% dextrose solution). On the left side of the front wall a solid state miniature signal generator (Mallory sonalert) was mounted and produced a sound of 80 db SPL.

Procedure. All animals were deprived of food for 23 hr before each experimental session. The rats and monkeys were shaped to press a lever and were reinforced for each lever press with a food pellet. After the initial training procedure, a VI schedule of reinforcement with a mean interval between scheduled reinforcements of 30 sec was installed. The intervals ranged from 5–60 sec. A 40 min session was scheduled daily. After the VI performance had stabilized, a 15 sec tone was presented two or three times during the session at irregular intervals. When the tone ceased to affect the ongoing VI behavior, the VI schedule and the tone presentations were discontinued for three days. During this period all rats were exposed to a fixed ratio 12 schedule with sweetened milk as reinforcements; the monkeys were reinforced by banana pellets on the same fixed ratio schedule during these days. Subsequent to this phase, the VI reinforcement contingency, using Noyes pellets, was again installed. The presentation of the tone (CS) was followed by the response-independent delivery of 0.5 ml sweetened milk or three banana pellets (US) for the rats and monkeys, respectively. For the length of the US presentation to the rats a 2.8 W bulb, mounted behind the spout, flashed. No stimulus accompanied the US presentation for the monkeys. After lever pressing during the CS was suppressed to about 15–30% of the control response rate during a 15 sec period immediately preceding the CS (PRE-CS), the drug injection schedule started.

The drugs were administered as outlined in Experiment 1. On the basis of the results from Experiment 1, the range of dosages was slightly altered. Generally, high dose levels which consistently produced profound depression of responding, and low doses which were without detectable behavioral effect were omitted. In comparison to Experiment 1, additional low dose levels of *d*-amphetamine and scopolamine hydrobromide and higher dosages of chlordia-

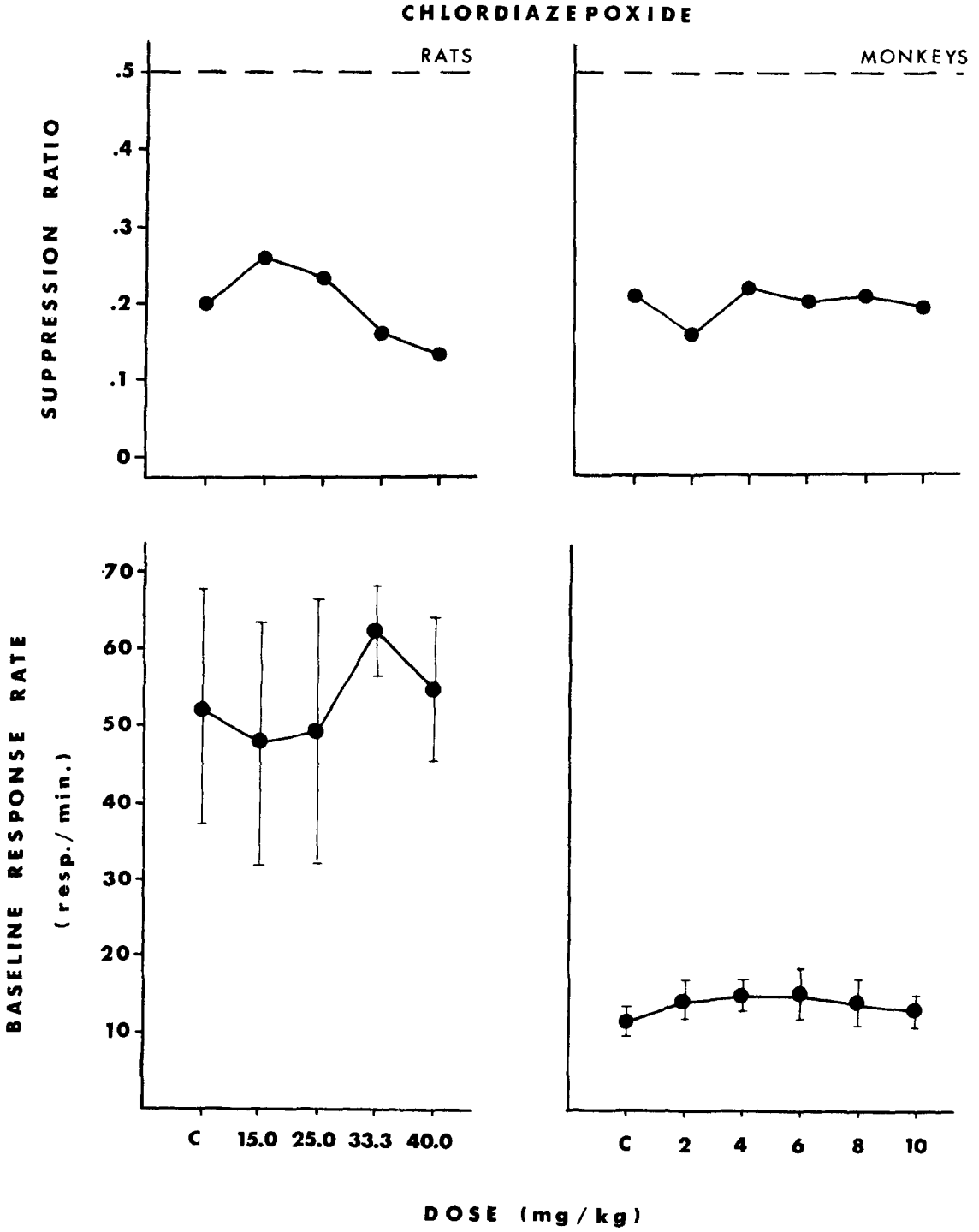

FIG. 3. Effects of chlordiazepoxide on the mean suppression ratio during a prereward stimulus (top) and the mean baseline response rate during a VI schedule of reinforcement (bottom) in rats (left half) and monkeys (right half). The vertical lines in the data points of the baseline response rate graphs (bottom) indicate the range of ± 1 S.E. from the mean rates of responding. "C" refers to the control condition after saline injections.

zepoxide were administered.

Results

Operant behavior was clearly suppressed during the presentation of the tone CS, that was followed by the delivery of the three free banana pellets (monkeys) or sweetened milk (rats). This type of conditioned suppression took 10–20 days to establish and was maintained over several months.

Chlordiazepoxide and diazepam did not change suppres-

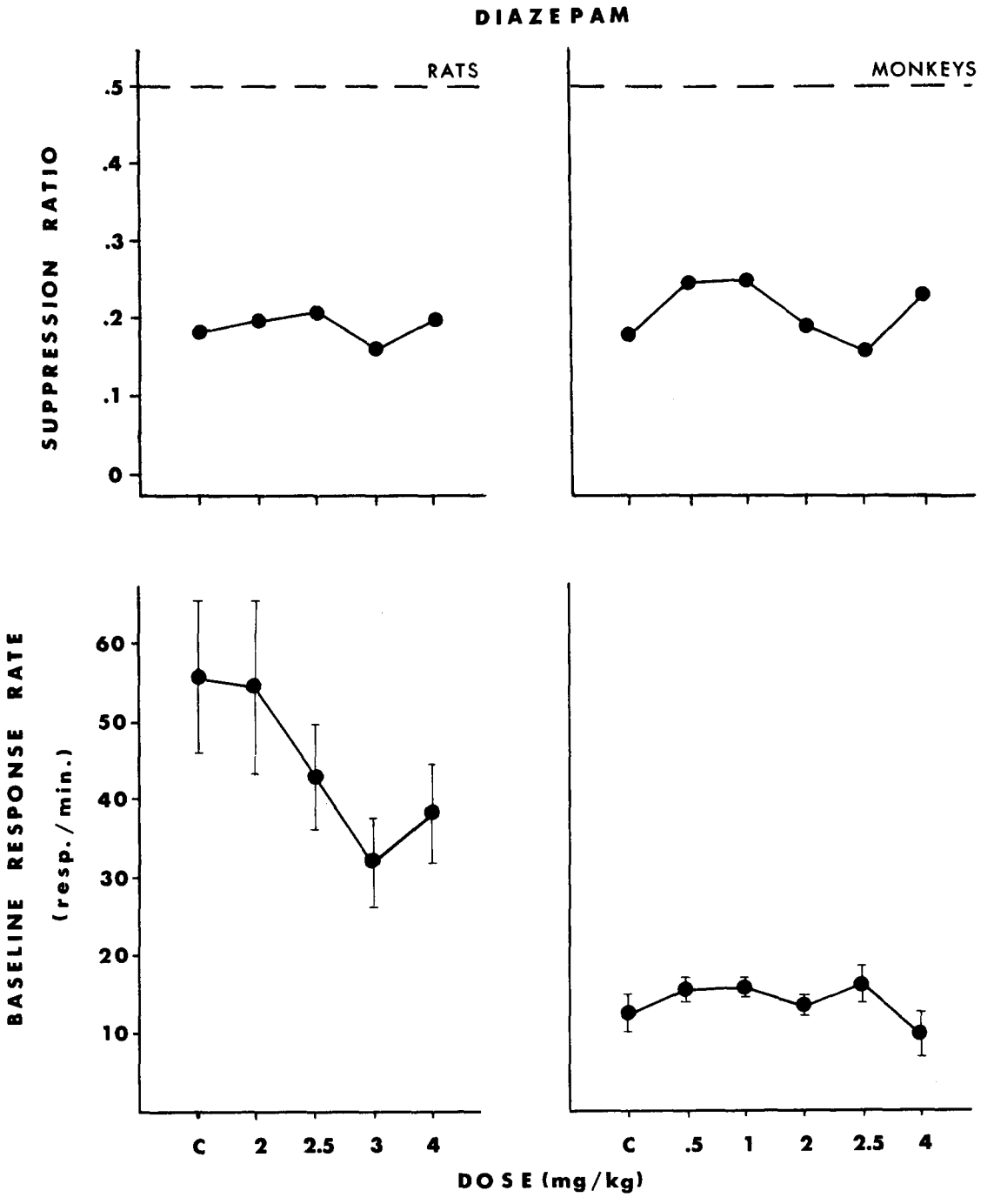

FIG. 4. Effects of diazepam on the mean suppression ratio during a prereward stimulus (top) and mean baseline response rate during a VI schedule of reinforcement (bottom) in rats (left half) and monkeys (right half). The vertical lines in the data points of the baseline response rate graphs (bottom) indicate the range of ± 1 S.E. from the mean rates of responding. "C" refers to the control condition after saline injections.

sion ratios at any dose level in either monkeys or rats (Figs. 3 and 4, top). Both benzodiazepine derivatives had no significant effect on overall session baseline response rates, when the rates of all animals were averaged (Figs. 3 and 4, bottom). However, both drugs increased VI baseline responding in several individual animals (Rats 72-847, 1081, 1082, Monkeys 67-2, 70-2, 70-3) between 20–80% from control sessions; baseline responding was unchanged or suppressed in the remaining animals. It is of special interest that conditioned suppression remained unaltered in all animals, although the drugs increased baseline responding in some of the animals and decreased it in others. The correlations between changes in baseline responding and those in conditioned suppression were nonsignificant.

Some doses of *d*-amphetamine consistently attenuated conditioned suppression in all rats; 0.33 mg/kg was the

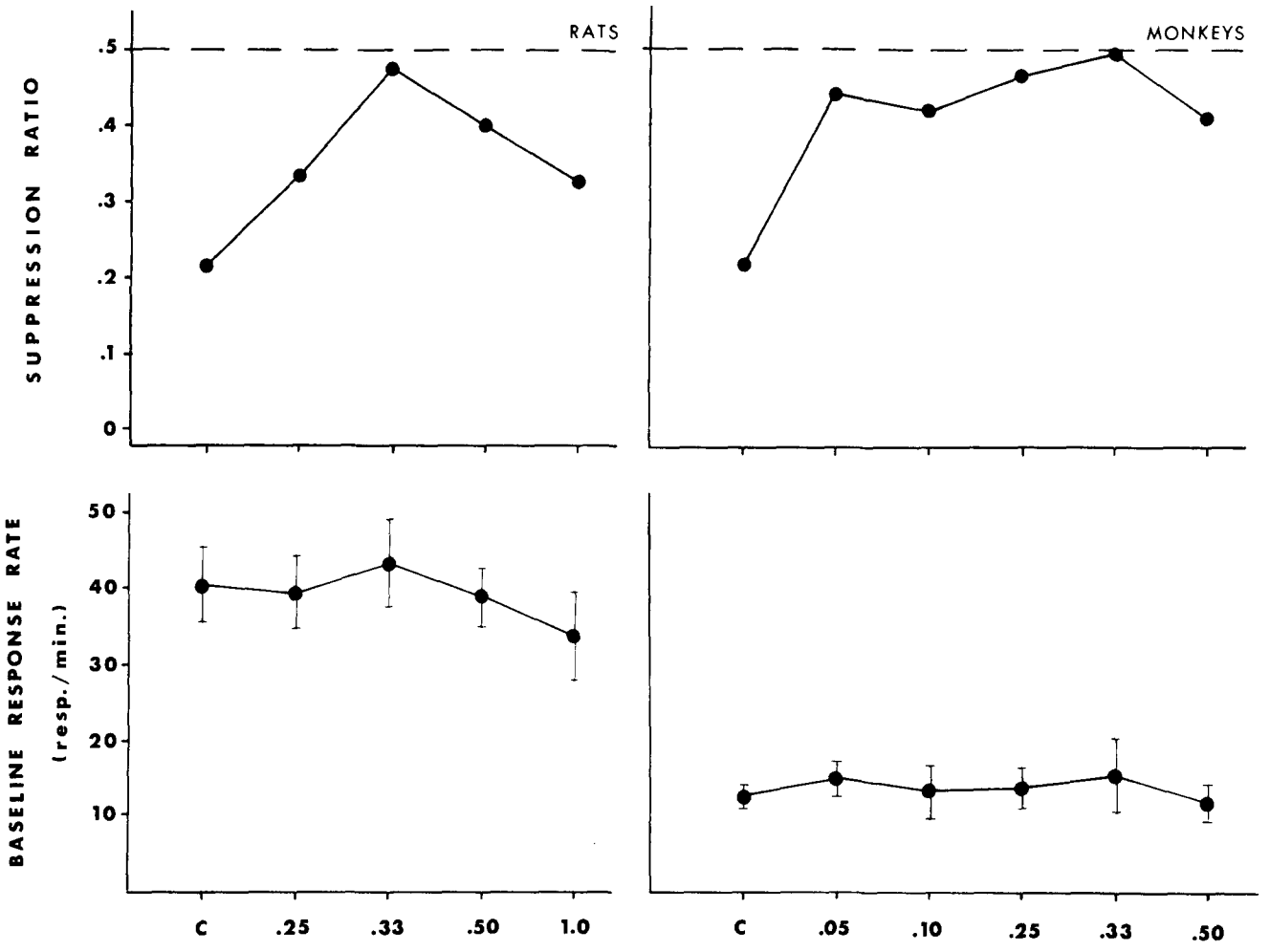

FIG. 5. Effects of *d*-amphetamine on the mean suppression ratio during a prereward stimulus (top) and the mean baseline response rate during a VI schedule of reinforcement (bottom) in rats (left half) and monkeys (right half). The vertical lines in the data points of the baseline response rate graphs (bottom) indicate the range of ± 1 S.E. from the mean rates of responding. "C" refers to the control condition after saline injections.

most effective dose (Fig. 5, left top). In the monkeys, administration of *d*-amphetamine, in doses ranging from 0.25–0.33 mg/kg, reduced conditioned suppression significantly (Fig. 5, right top). In three of the six rats and in all monkeys the attenuation of conditioned suppression was accompanied by a slight, but nonsignificant enhancement of baseline responding (Fig. 5, bottom). No significant correlation was found between the magnitude of both effects of *d*-amphetamine.

Scopolamine hydrobromide and its quaternary amine derivative did not disinhibit the suppressed behavior during the CS at any dose level in any monkey or rat (Fig. 6, top). All lever-pressing was significantly decreased at the higher doses ($p<0.05$ and $p<0.01$) (Fig. 6, bottom). At higher dose levels of scopolamine hydrobromide, the monkeys as well as some of the rats did not consume the food pellets presented as US or as reinforcements on the VI schedule.

Discussion

In confirmation of earlier reports [3,32] it was found that conditioned suppression of operant behavior can be produced by conditioned stimuli which terminate contiguously with noncontingent positive stimuli. Other investigators [9, 21, 22, 27] have observed a facilitation of operant responding during the presentation of prereward stimuli, but the latter studies used different experimental parameters and procedures which may have permitted superstitious conditioning and insufficient stimulus control.

The general disinhibitory effects that are often attributed to scopolamine and the benzodiazepine derivatives were not observed in the present experiments. Both drugs failed to disinhibit responding suppressed by a CS which preceded a positive stimulus in monkeys as well as in rats. On the other hand, the benzodiazepines facilitated significantly baseline responding in several rats and all monkeys which responded at low rates. Scopolamine consistently impaired baseline lever pressing. The effects of chlordiazepoxide differ from those found in the preceding experiment on aversive conditioned suppression and in punishment experiments [31]. At certain dose levels (25–40 mg/kg in rats), chlordiazepoxide enhanced the rate of aversively suppressed behavior, but failed to attenuate conditioned suppression induced by a signal preceding a positive US.

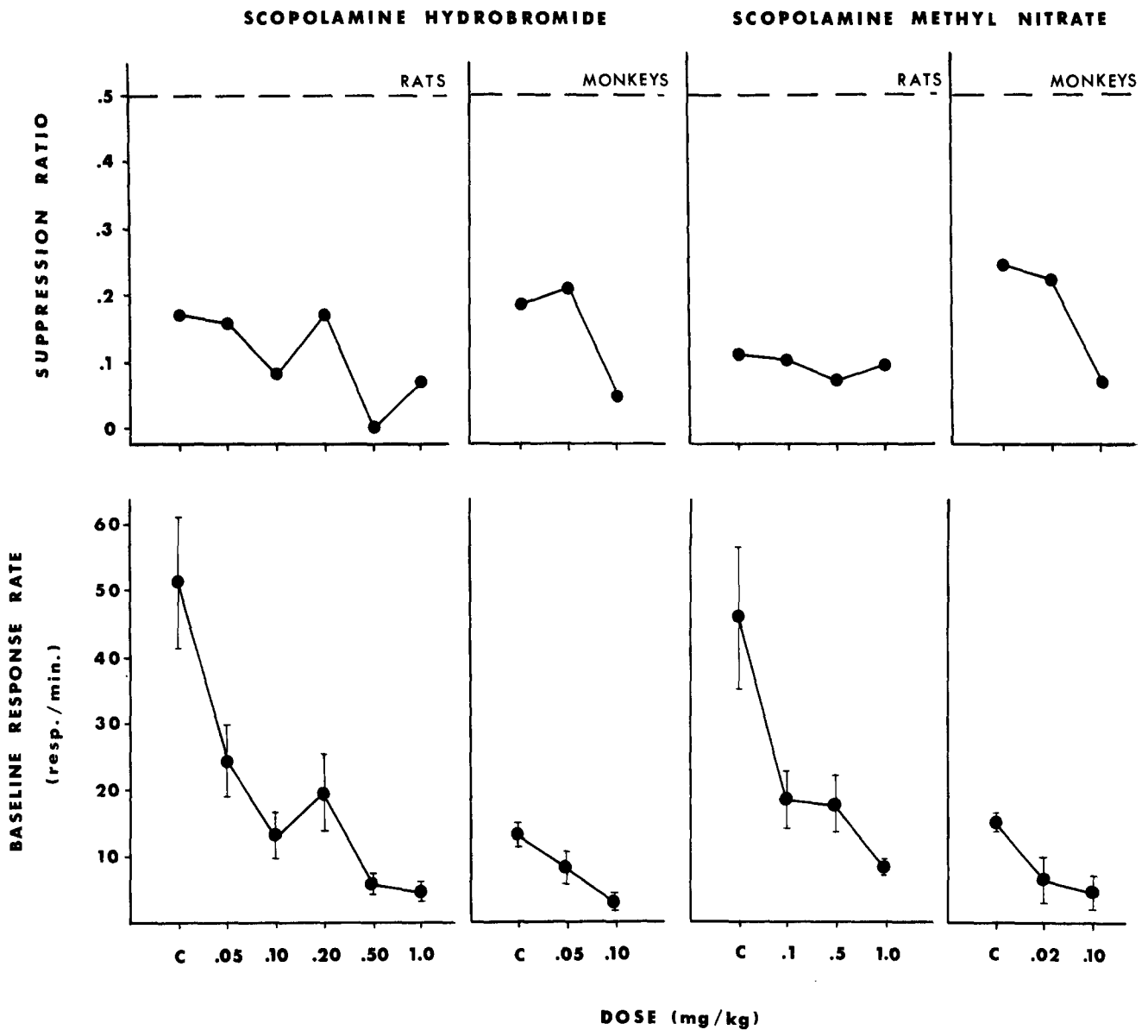

FIG. 6. Effects of scopolamine hydrobromide and scopolamine methyl nitrate on the mean suppression ratio during a prereward stimulus (top) and the mean baseline response rate during a VI schedule of reinforcement (bottom) in rats and monkeys. The vertical lines in the data points of the baseline response rate graphs (bottom) indicate the range of ± 1 S.E. from the mean rates of responding. "C" refers to the control condition after saline injections.

In spite of the apparent similarities between the types of behavioral suppression produced in Experiments 1 and 2 certain procedural differences limit somewhat a direct comparison of the drug effects in both experiments. Both kinds of conditioned suppression are highly sensitive to parametric changes [1, 2, 28, 32]. For example, in the present experiments only the animals in the positive conditioned suppression paradigm had experience with the US, before being subjected to CS-US presentations. However, in order to establish that sweet milk (for the rats) or banana pellets (for the monkeys) could serve as potent reinforcers, it appeared warranted to use these stimuli as reinforcers in a test situation which was different from the conditioned suppression paradigm. This additional experience for the subjects in the second experiment might have contributed to the differential drug effects in the two experiments. Furthermore, the parameters of the CS-US presentations differed in both experiments. In the first experiment the presentation of a 20 sec continuous light served as CS, whereas in the second experiment a 15 sec tone was used as CS. Since parametric manipulations of the conditioned suppression procedures were not performed, it is possible that these procedural differences might have influenced the differential action of chlordiazepoxide and amphetamine in both paradigms.

It has recently been suggested that the rate-enhancing effects of the benzodiazepine derivatives in aversive experimental situations may be due to a general facilitatory or

disinhibitory effect on behavior in any situation which generates low rates of responding rather than to a selective action on aversively suppressed behavior [29,39]. The results of the present experiment indicate that, in addition to these general facilitatory properties, the benzodiazepines seem to have a more specific effect on behavior which is suppressed by preshock stimuli. This conclusion also is supported by Cook and Catania's [13] and Miczek's [31] observations that increasing doses of chlordiazepoxide enhanced the rate of punished operant behaviors more effectively than that of nonpunished behavior.

It is possible that the appetite stimulating properties of the benzodiazepine derivatives may account, in part, for the facilitatory effects of these drugs. The rate-enhancing effects on food-reinforced behavior could possibly be explained by the drugs' potentiating effect on food and water consumption [30]. However, chlordiazepoxide's failure to increase responding during a CS which preceded the presentation of a free food reward argue against the generality of this interpretation.

Amphetamine markedly enhanced responding during the presentation of a prereward stimulus and also increased baseline responding slightly in most rats and all monkeys. These results contrast with those found in Experiment 1, where amphetamine failed to facilitate responding during the presentation of a preshock stimulus (although the baseline rate of responding was elevated). It is well known that amphetamine increases operant responding under many conditions which generate low rates of responding [14, 31, 35]. It does not eliminate the response suppression to a preshock stimulus (Experiment 1) or to punishment [18,31]. This pattern of effects suggests that amphetamine facilitates responding in situations which generate low rates of responding but do not involve aversive stimuli. However, recently it has been demonstrated that low doses of amphetamine may even increase responding suppressed by punishment [31].

In spite of certain differences between the procedures in Experiments 1 and 2, the presently observed paradigm-dependent drug effects may have implications for our understanding of the conditioned suppression phenomenon itself. The fact that prereward as well as preshock stimuli can elicit conditioned suppression of ongoing operant behavior suggests that suppression of lever pressing may not be a valid index of anxiety or fear as suggested by Estes and Skinner [15] and others. The finding that the benzodiazepine derivatives as well as amphetamine generally produce opposite effects on response suppression in the present paradigms when the physical quality of the unconditioned stimulus was changed indicates further that unitary explanations of the phenomenon, such as inhibition [12] or a general emotional state [3], may not adequately account for the response suppression in the two apparently similar paradigms.

The differential effects of amphetamine and the benzodiazepines indicate that basically different phenomena may be involved in the two conditioned suppression paradigms. An interpretation of the conditioned suppression phenomenon in terms of the superimposition of classical conditioning procedures on ongoing operant behavior [32] accommodates these observations, suggesting that a prereward stimulus elicits topographically different behaviors than does a preshock stimulus. In addition, it is possible to relate response suppression during a signal which precedes free reinforcement to the recent findings that presentation of response-independent reinforcement decreases operant behavior (e.g., [6]). A stimulus preceding reinforcement which is presented independent of lever pressing seems to control primarily behaviors other than operant lever pressing. These non-lever-pressing behaviors may be differentially susceptible to the action of amphetamine and chlordiazepoxide.

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