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Phenobarbital and d-Amphetamine Effects on Discrimination Performance of Rats and Juvenile Baboons[1]

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GELLER, I., R. J. HARTMANN AND E. MORAN. *Phenobarbital and d-amphetamine effects on discrimination performance of rats and juvenile baboons.* PHARMACOL BIOCHEM BEHAV **18**(1) 107–113, 1983.—Hungry rats in Skinner boxes were trained to select the right or left lever as correct as a function of the presence of a tone or light stimulus, respectively. Correct responses produced liquid food rewards. Acute intraperitoneal administration of d-amphetamine or phenobarbital did not affect accuracy of performance, but decreased the percent trials attempted and lengthened response times as a function of increasing doses. The mean extra responses during the delay intervals generally decreased under phenobarbital and increased under d-amphetamine. Juvenile baboons were trained to respond on a delayed match-to-sample task in order to obtain banana pellet rewards. Acute intramuscular administration of phenobarbital produced a dose-related increase in errors, a decrease in mean extra responses and an increase in response times. A slight reduction in the percent trials attempted occurred only at the highest dose of the drug. Acute intramuscular d-amphetamine did not increase errors even at dose levels that increased reaction times, decreased extra responses and reduced the percent trials attempted.

Discrimination Delayed match-to-sample Phenobarbital d-amphetamine

A NUMBER of studies have demonstrated the value of discrimination tasks for the study of neuroactivity of chemical agents in animals [2, 3, 4, 5]. Discrimination tasks have the advantage of simultaneously providing measurements of a number of different parameters. These include accuracy of performance, response times, percent of trials attempted and number of extra inconsequential responses. Such studies have been conducted with rats [2,10], pigeons [13,14], rhesus monkeys [1,6] and juvenile baboons [3,5]. A necessary requirement for the application of discrimination tasks for the evaluation of new chemical agents is the establishment of an appropriate data base with representative central nervous system (CNS) active compounds about which considerable pharmacological and toxicological data are available. The intent of the present investigations was an evaluation of two such compounds: d-amphetamine, a CNS stimulant, and phenobarbital, a CNS depressant [7,17]. The drugs were administered to laboratory rats trained on a discrimination task and to juvenile baboons trained on a delayed match-to-sample discrimination task.

METHOD

Experiment 1

The subjects were Holtzman male Sprague-Dawley rats 60–90 days old at the start of the experiment. They were gradually reduced to 80% of their original starting weights and were thus maintained throughout the course of the experiment by limited feedings following each behavioral test session. The method for training animals on the discrimination task has been described previously [3,4]. Briefly, it was as follows: the hungry rats were placed in Skinner boxes for one-half hour during which time the feeders were activated every 90 seconds to deliver the liquid food reward. On the following 3 days the rats were placed in the test chambers and were given access only to the left lever. Pressing this lever activated a light stimulus and also produced a food reward. The rats remained in the chamber for one-half hour or until they made 100 responses. The right lever was then substituted for the left lever and the animals received similar training in which a tone stimulus was paired with lever presses. After 3 days on this procedure, acquisition training for the discrimination task began. A variable-interval tape programmer was employed to activate tone or light stimuli in a mixed order on the average of once every 2 minutes (2-min VI). The tape programmer was stopped during tone or light stimuli; pressing the correct lever turned off the stimulus and activated the milk feeder. Pressing the incorrect lever simply turned off the stimulus. When no responses occurred, the stimuli remained on for a 60-second period. At the termination of the stimuli presentations, the VI tape programmer was started again. The final conditions for performance of

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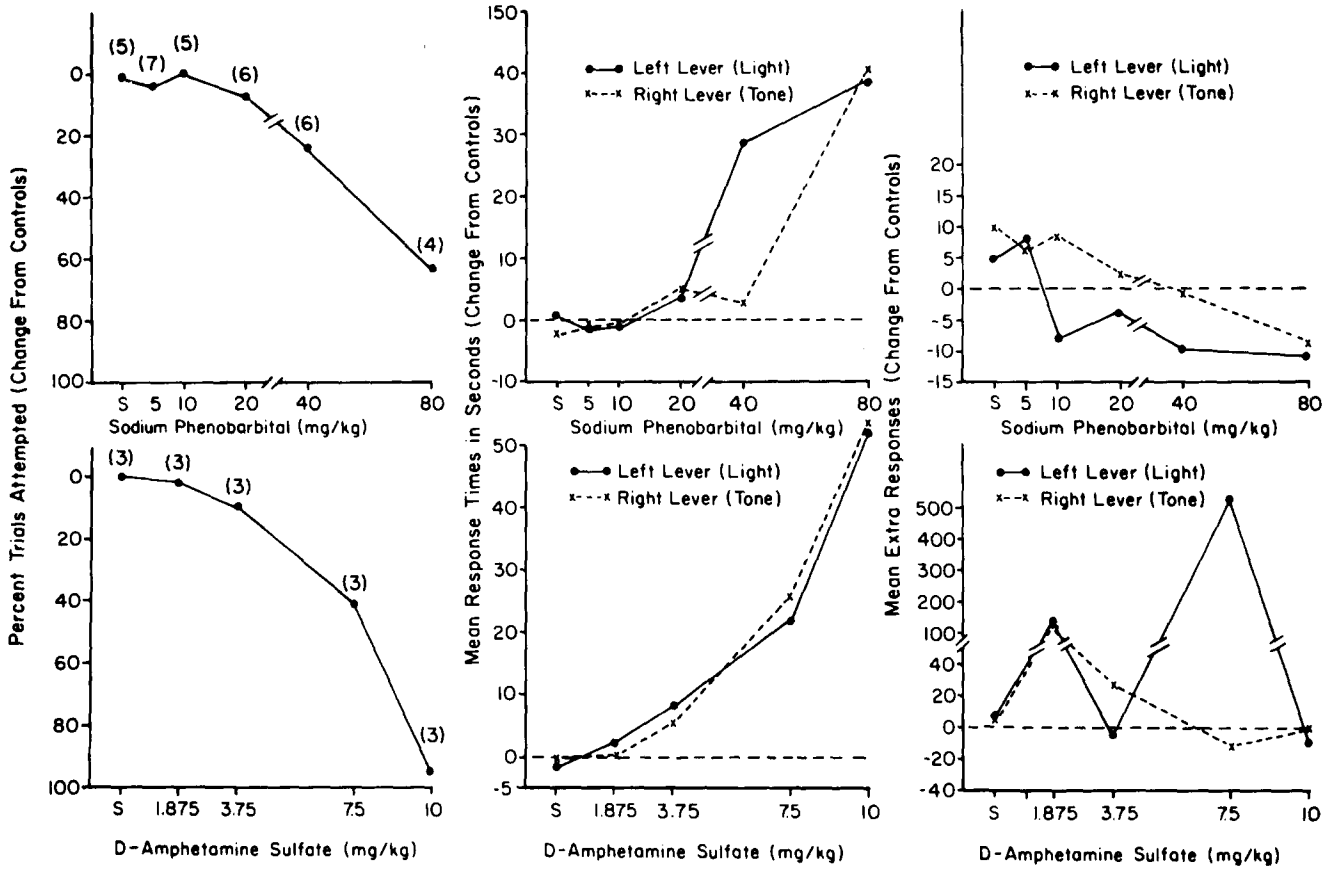

FIG. 1. Effect of acute administration of sodium phenobarbital and d-amphetamine on discrimintion performance of rats. Numbers in parentheses in the first panels represent the number of animals treated at each dose level. The points on the graphs are difference scores between the group means under drug and pre-drug conditions. The extra responses represent averages across animals of total responses per session.

the discrimination task required that hungry rats select the right or left lever as correct as a function of the presence of a tone or light stimulus, respectively. Experimental sessions of 1-hr duration were conducted on Monday through Friday of each week.

The behavioral measures recorded were: errors per session; percent trials attempted (which reflects degree of inability or disinterest in responding to stimuli); mean response times on either the right or left lever (i.e., how long it took the animal to respond following onset of a stimulus); and extra inconsequential responses which occurred during the session in the absence of the discriminative stimuli.

Drug preparation and administration. The doses of d-amphetamine were calculated as the sulfate and phenobarbital as the sodium salt. The drugs were dissolved in 0.9% saline and were administered intraperitoneally in a volume of 1 ml/kg body weight, 30 minutes prior to a behavioral test session. Groups of animals trained on the discrimination task were administered either saline or one of the drugs at one of the following dose levels: d-amphetamine at 1.875, 3.75, 7.5 or 10 mg/kg or phenobarbital at 5, 10, 20, 40 or 80 mg/kg.

Experiment 2

Four young male baboons (*papio anubis*), obtained from the breeding colonies at Southwest Foundation, were used as subjects. Training on the match-to-sample (MTS) task was accomplished with an intelligence panel mounted on one wall of each animal's cage. The panel contained a row of three translucent discs upon which could be projected stimuli of varying shapes; under the appropriate experimental conditions, pressing either of the side discs produced a banana pellet reward which appeared in a small hopper mounted on the panel beneath the three discs. A stimulus was projected on the center lever aperiodically on the average of once every 3 minutes throughout an experimental session. Two minutes after this stimulus was turned off (delay interval), stimuli were projected on the two side discs; one of these side stimuli matched the one presented on the center disc 2 minutes earlier and pressing the matching stimulus terminated the stimuli and produced a banana pellet reward. Pressing the incorrect stimulus simply terminated the stimuli. The correct matching stimulus was varied between the side discs in a mixed order. The method for training baboons on the MTS task has been described in detail [3,5].

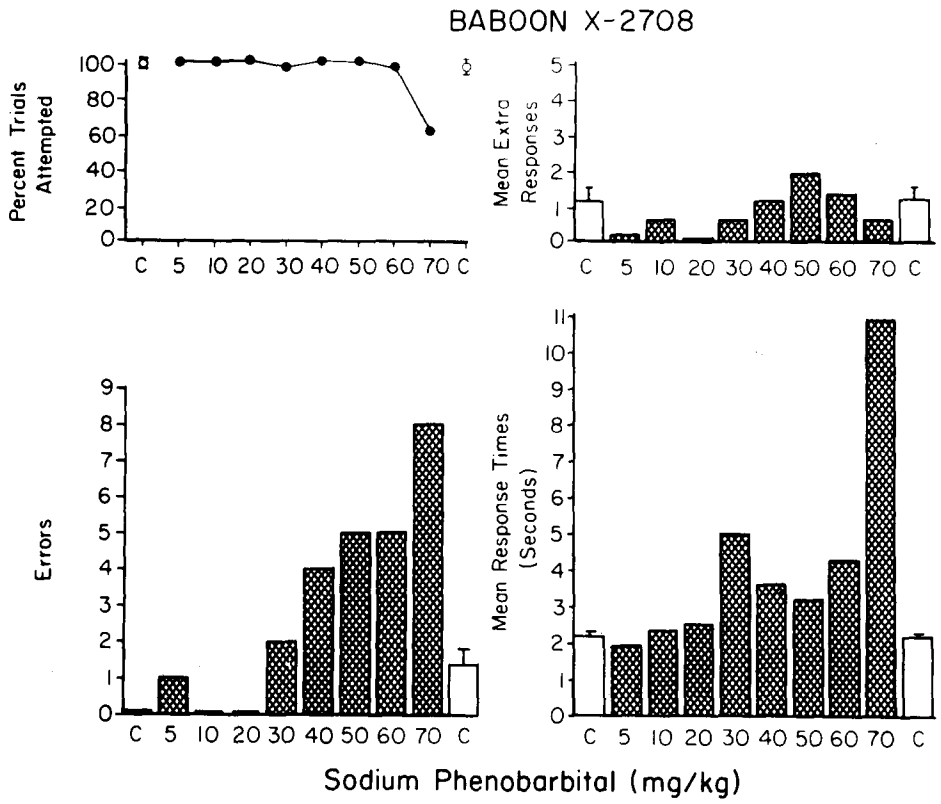

FIG. 2. Effects of acute sodium phenobarbital on a delayed match-to-sample task in the juvenile baboon. Open bars or open circles indicate averages for the pre- and post-drug controls. Brackets represent standard errors of the mean. Solid circles and stippled areas show the data obtained at the different treatment levels. Mean extra responses represent average responses per delay interval for an experimental session.

Experimental sessions of 2-hr duration were conducted on Monday through Friday of each week. Programming of experiments and recording of data were accomplished with a distributed microprocessor computer system. Records were kept of the total number of trials (center stimuli), the number of trials attempted by each animal, the number of correct responses on the side levers, the average number of extra responses per trial (responses made on any lever during delay intervals) and how long it took a subject to respond after the side stimuli were activated (response times).

Drug preparation and administration. The drugs were prepared as in Experiment 1 and were administered intramuscularly in a volume of 1 ml/kg body weight one-half hour prior to a behavioral test session. The drug administrations were separated by at least one week. All subjects were administered first a series of phenobarbital injections in doses ranging from 5.0 mg/kg to 70 mg/kg. The order of drug injections was generally from the lowest to the highest dose. Six weeks after completion of the phenobarbital experiment, the animals were injected with d-amphetamine at 0.05, 0.10, 0.25 and 0.5 mg/kg. The amphetamine injections were given in a mixed order so that the sequence of doses was different for each animal.

RESULTS

Experiment 1

Neither phenobarbital nor amphetamine had any effect on accuracy of performance in the rat experiment. Acute administration of either drug produced no change in error scores relative to the previous day's control data. The other three parameters, represented in Fig. 1, were obtained by determining the group mean effects under drug and pre-drug conditions and calculating the difference scores between them; this value is referred to as change from control. At 40 mg/kg phenobarbital, the rats responded to 25% fewer stimuli than during the pre-drug control session. At 80 mg/kg the difference between the control and drug values was 63%. Under d-amphetamine, the mean percent trials attempted varied as a function of the dose. The downward changes from the control values were 10% at 3.75 mg/kg, 41% at 7.5 mg/kg and 94.7% at 10 mg/kg.

The response time data has been broken down into left lever (light) responses or right lever (tone) responses. At 20 mg/kg phenobarbital, response times were lengthened on the left lever to 3.5 seconds and on the right lever to just over 5 seconds. At 40 mg/kg phenobarbital, response times on the

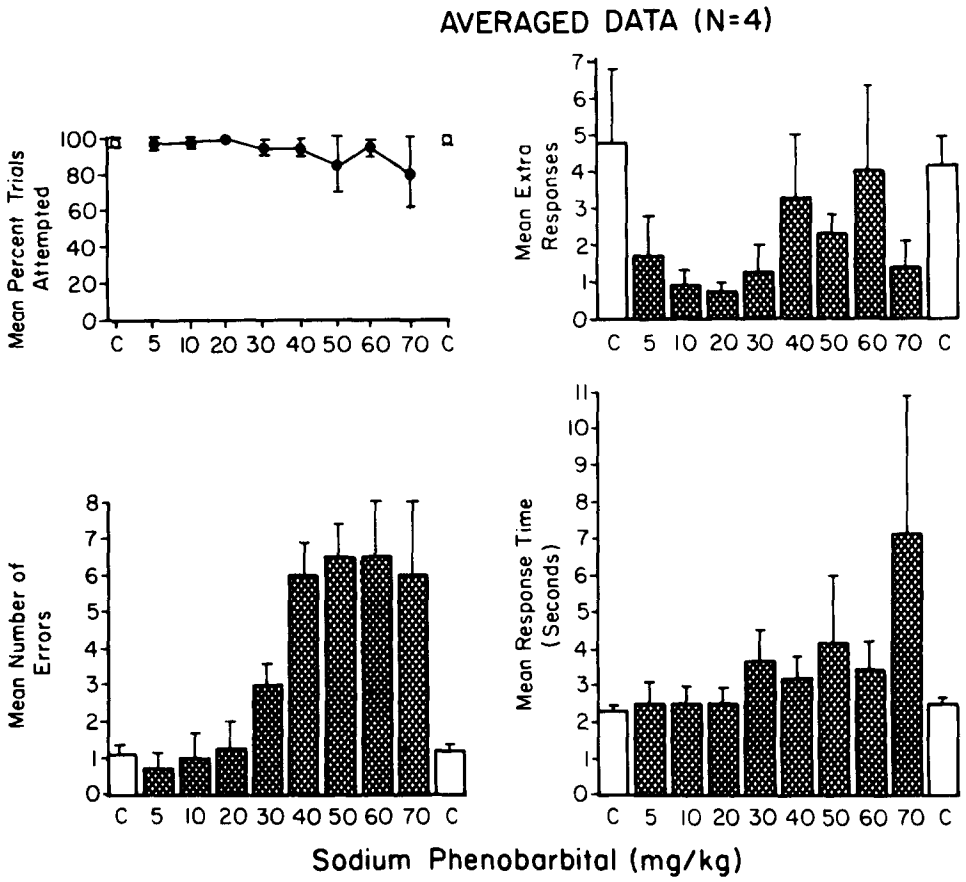

FIG. 3. Effect of acute sodium phenobarbital on a delayed match-to-sample task in juvenile baboons. Open bars or open circles indicate averages for pre- and post-drug controls. Brackets represent standard errors of the mean. Solid circles and stippled areas show the data obtained at the different treatment levels. Extra responses are expressed as mean extra responses per delay interval.

left lever reached 28.7 seconds while response times on the right lever dropped to 3 seconds. The highest dose of the drug increased response times on the left lever to 38.5 seconds and on the right lever to 40.7 seconds. Under d-amphetamine, the mean response times increased on both levers in a dose-related manner. Increases on the left and right levers respectively were 8.2 and 5.5 seconds at 3.75 mg/kg, 22.7 and 26 seconds at 7.5 mg/kg and 52 and 54 at 10 mg/kg d-amphetamine.

The mean extra responses on the left lever increased under saline and the 5 mg/kg dose of phenobarbital and decreased at all other dose levels. The mean extra responses on the right lever decreased at the 40 and 80 mg/kg dose of phenobarbital and increased under saline and at all other dose levels. The mean extra responses were affected similarly on both levers under the two low doses of d-amphetamine; however at 7.5 mg/kg d-amphetamine, the change in extra responses on the left lever (light) was greater than 500 above control while it was 10 less than control on the right (tone) lever.

Experiment 2

Figure 2 contains data obtained for a representative baboon on each of the behavioral parameters during control and under phenobarbital. The mean control data (open bars or circles) and standard errors of the means were obtained by averaging all the data obtained during the pre-drug control sessions or during the post-drug control sessions. Administration of saline on four occasions yielded averaged data like that of the no-treatment control averages. The percent trials attempted by baboon 2708 remained in the control range under all doses of phenobarbital except the highest dose of 70 mg/kg where it dropped to the 60% level. Errors increased from a control value of 0 to a maximum of 8 at the highest dose of phenobarbital. Extra responses remained in pre- and post-drug control ranges under all doses of the drug. An increase of mean response times occurred at doses of phenobarbital greater than 20 mg/kg. Similar data averaged for four animals are shown in Fig. 3. The means and standard errors of the means were obtained by averaging the data for eight pre- or post-exposure control sessions for each animal as well as for the specific dose levels of drug for the four animals. (The 70 mg/kg data was derived from only two of the subjects). The open bars and circles represent the control averages under each dose of the drug. It is of interest that the data obtained under saline (not shown) and averaged across animals yielded values very similar to the control averages

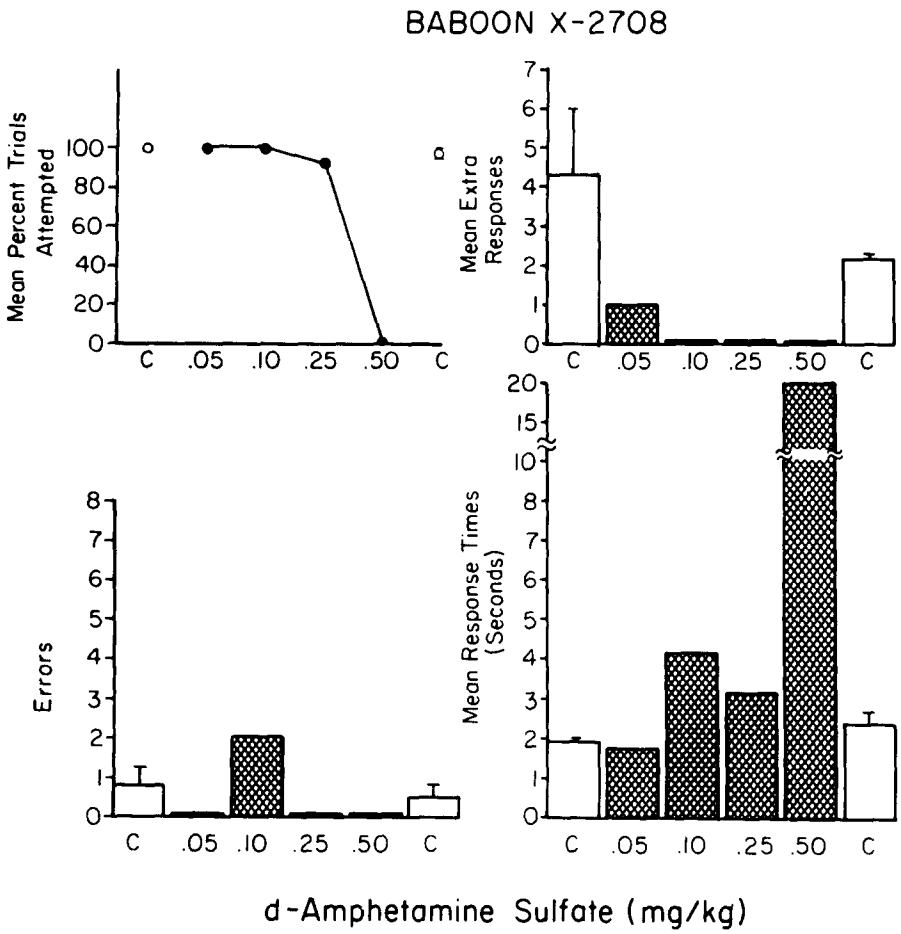

FIG. 4. Effect of acute d-amphetamine sulfate on a delayed match-to-sample task in the juvenile baboon. Open bars or open circles indicate averages for the pre- and post-drug controls. Brackets represent standard errors of the mean. Solid circles and stippled areas show the data obtained at the different treatment levels. Extra responses are expressed as mean extra responses per delay interval.

shown in the figure: 1.08 errors, 2.33 seconds for response times, 2.24 for extra responses and 100 for percent trials attempted. The group average percent trials attempted remained in the control range under all doses of the drug. The mean number of errors increased from a control average of 1.1 to a maximum of 6.5 errors at the 50 and 60 mg/kg dose levels. The mean extra responses were reduced below the control averages at all doses of phenobarbital excepting the 40 and 60 mg/kg levels where extra responses were in the pre- and post-drug control ranges.

Figure 4 contains data showing the effects of four doses of d-amphetamine on the MTS task in the same baboon. The control means and standard errors of the means were obtained by averaging the pre- or post-drug control data for each dose level of d-amphetamine. The percent trials attempted were relatively unaffected until the 0.5 mg/kg dose of d-amphetamine when the value was reduced to zero. Errors were generally unaffected under the drug with the exception of the 0.10 mg/kg dose where errors increased to 2 from a control average value of 0.75. Under 0.05 mg/kg d-amphetamine mean extra responses were reduced to 1 from a control average of 4.34 and to 0 at all other dose levels. At 0.1 mg/kg and above, mean response times increased above the control values reaching a maximum of 20 at the 0.5 mg/kg dose level. The averaged data for the four baboons, shown in Fig. 5, are very similar to those of the individual animal. The percent trials attempted were reduced to 73.3 under 0.25 mg/kg of the drug and to 39.8 under 0.5 mg/kg. The mean number of errors under each dose of the drug remained in the pre- and post-drug control ranges while the average number of extra responses was reduced to less than 1 under all dose levels of the drug. Mean response times increased at doses of d-amphetamine of 0.1 mg/kg and above and reached a maximum of 13.2 under 0.5 mg/kg of the drug.

DISCUSSION

Phenobarbital produced a dose-related increase in the mean number of errors on the baboon match-to-sample task but had no effect on errors in the rat discrimination task at dose levels including those that reduced the percent trials attempted. Response times on the baboon match-to-sample

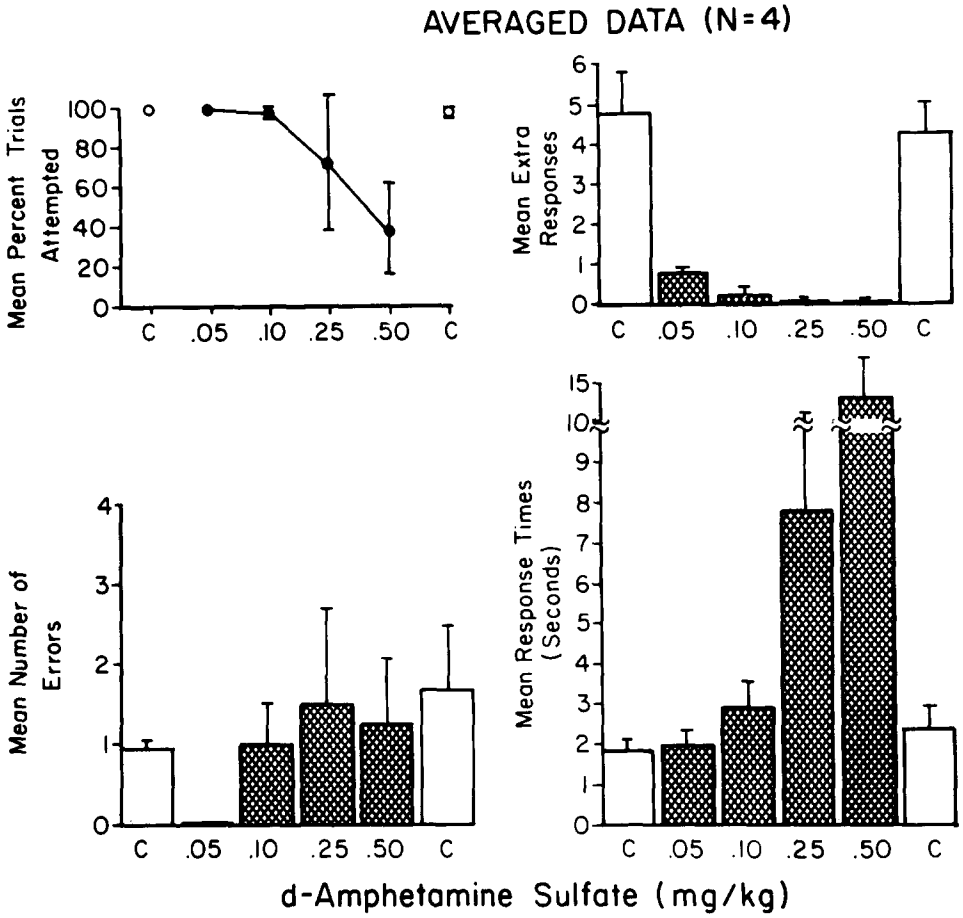

FIG. 5. Effect of acute d-amphetamine on a delayed match-to-sample task in juvenile baboons. Open bars or open circles indicate averages for pre- and post-drug controls. Brackets represent standard errors of the mean. Solid circles and stippled areas show the data obtained at the different treatment levels. Extra responses are expressed as mean extra responses per delay interval.

task increased at doses above 20 mg/kg while mean extra responses during the delay intervals were decreased at most dose levels of the drug. Response times on the rat discrimination task also increased as a function of increasing dose.

d-Amphetamine did not increase errors on the baboon MTS task at dose levels that reduced the mean percent trials attempted. Similarly, the rat discrimination task yielded data indicating no effects on errors at doses that decreased the percent trials attempted. The absence of this amphetamine effect upon accuracy in both rats and baboons cannot be attributed to ineffective dosing, since the doses administered were high enough to affect other measures in addition to the percent trials attempted. Under d-amphetamine, response times on the MTS task increased as a function of dose while the mean extra responses during delay intervals were reduced below the pre- and post-drug control levels. Similar effects were produced on the rat discrimination task in that the response times increased as a function of dose. However, extra responses for the rats increased at the 1.875 and 7.5 mg/kg dose levels.

The baboon data are in agreement with those of several investigators. McMillan *et al.* [13,14] reported on the effects of pentobarbital and d-amphetamine on a delayed matching to sample task in pigeons. Pentobarbital decreased accuracy of responding at 3.0 and 5.6 mg/kg, doses that did not affect latencies or rates of responding on any of three response keys, while d-amphetamine did not affect matching accuracy at 0.1–1.0 mg/kg, doses that did reduce rates of responding and increase response latencies. Roberts and Bradley [16] reported that administration of 5.0 mg/kg pentobarbitone to African green monkeys, trained on a delayed visual discrimination task, caused a significant reduction in accuracy of responding.

A number of other investigators have reported effects with amphetamine in rats or rhesus monkeys that are not in agreement with the findings of the present experiments. Glick and Jarvik [6] found that 0.1, 0.2 and 0.4 mg/kg of d-amphetamine decreased accuracy of performance of rhesus monkeys working on a delayed MTS task for water rewards. Bauer and Fuster [1] reported that administration of 0.2 and 0.4 mg/kg d-amphetamine to rhesus monkeys performing on a delayed MTS task reduced the percentage of correct responses, increased motor activity and shortened reaction times on the choice levers at the 0.4 mg/kg dose.

Kesner *et al.* [8] reported that administration of 0.33–3.0 mg/kg d-amphetamine to rats produced a disruption of a delayed alternation and a spatial match-to-sample task.

Several studies have indicated a relationship between the effects of amphetamine on behavior and the degree of stimulus control that is exerted on the behavior. Laties [11] demonstrated that drug effects on behavior may be modified by external discriminative stimuli. Pigeons trained on a fixed consecutive number schedule had to make a fixed number of responses on one key and then switch to a second key to obtain reinforcement. Administration of d-amphetamine resulted in premature switching to the reinforcement key before completion of the fixed number response requirement. Addition of a discriminative stimulus to signal completion of the fixed number requirement reduced the effects of d-amphetamine on the behavior. Laties *et al.* [12] have recently replicated these findings in the rat. In this study not only was the d-amphetamine effect diminished but there was also evidence of a possible increase in discriminative stimulus control under d-amphetamine.

Ksir [9] trained rats on a two-lever-choice discrimination task to respond to the brighter of two response keys. When only one key was illuminated, the task was relatively easy. The difficulty of the task was increased by illuminating the second no-light lever with stimuli of varying intensity. d-Amphetamine produced no increase in errors when the behavior was under strong stimulus control (light/no-light situation). The addition of light stimuli of varying intensity to the no-light lever resulted in weaker stimulus control of the behavior. Under these conditions d-amphetamine produced a dose related increase in errors.

In a more recent study with the same experimental paradigm, 0.5–2.0 mg/kg amphetamine reduced correct responses with a greater effect on difficult than on easy trials. The highest dose of phenobarbital, 16 mg/kg, reduced the correct responses on difficult but not on easy trials despite the fact that the percent trials responded to was reduced on both easy and difficult trials at this dose [10]. Since the baboons in the present studies received all phenobarbital administrations first, they may have been better trained during the d-amphetamine phase of the experiments. In view of the findings of the above cited studies [9, 10, 11, 12], this might account for the lack of d-amphetamine effects on accuracy in the present experiment.

These experiments show that two pharmacological agents which are representative of two different classes of compounds, central nervous system stimulants [7] and depressants [17], differentially affect performance of animals on discrimination tasks under the conditions of these experiments. Discrimination performance in the rat is not affected under acute phenobarbital or d-amphetamine at doses that increase response times and reduce the percent responses to stimuli. On the delayed match-to-sample task in baboons, phenobarbital increases errors and d-amphetamine does not when the drugs are administered at doses that affect other measures. Both drugs lengthen response times while d-amphetamine seems to have a more pronounced effect in reducing extra responses. This may be due to a d-amphetamine-induced increase in competing behaviors other than lever pressing. The differential effects observed between drugs in the baboon and with the same drugs between different species of animals may be due to the degree of task difficulty or the degree of stimulus control exerted on the behavior.

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