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Acute Effects of *d*-Amphetamine in a Monkey Operant Behavioral Test Battery

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SCHULZE, G. E. AND M. G. PAULE. *Acute effects of* d-*amphetamine in a monkey operant behavioral test battery*. PHARMACOL BIOCHEM BEHAV **35**(4) 759–765, 1990.—The acute effects of *d*-amphetamine were assessed using a battery of complex food-reinforced operant tasks that included responding in delayed matching-to-sample (DMTS, n = 6), conditioned position responding (CPR, n = 7), progressive ratio (PR, n = 8), temporal response differentiation (TRD, n = 4), and incremental repeated acquisition (IRA, n = 9) tasks. Performance in these tasks is thought to depend upon specific brain functions such as short-term memory and attention (DMTS), color and position discrimination (CPR), motivation to work for food (PR), time perception (TRD), and learning (IRA). *d*-Amphetamine sulfate (0.01–1.0 mg/kg IV), given 15-min presession produced significant dose-dependent decreases in the number of reinforcers obtained in each task. Response accuracy was significantly decreased at doses of 0.3 and 1.0 mg/kg for TRD and at 1.0 mg/kg for CPR when compared to saline injections. Accuracy was not consistently affected in the DMTS or IRA tasks. Response rates decreased or response latencies increased significantly at doses of 0.3 and 1.0 mg/kg in the PR and DMTS tasks. A dose of 0.1 mg/kg for the IRA and TRD tasks, 0.3 mg/kg for DMTS and 1.0 mg/kg for the CPR tasks significantly decreased percent task completed. Thus, the relative sensitivities of these tasks for detecting *d*-amphetamine behavioral effects were IRA = TRD > PR = DMTS > CPR. These results indicate that in monkeys, performance of operant tasks designed to model learning ability and time perception is more sensitive to the disruptive effects of *d*-amphetamine than is performance in tasks designed to model motivation, short-term memory and attention, which is more sensitive than tasks that model color and position discrimination.

d-Amphetamine Monkeys Operant test battery

d-AMPHETAMINE, a centrally active sympathomimetic, produces a variety of effects on behavior and the CNS by enhancing presynaptic catecholamine release thus facilitating catecholamine neurotransmission (20,24). Some behavioral effects of *d*-amphetamine are well documented. For example, in rats low doses of *d*-amphetamine typically increase locomotor activity while high doses induce stereotypy (3,4). Generally, *d*-amphetamine decreases the high rates of responding generated by fixed-ratio schedules and increases low rates of responding generated by fixed-interval schedules of reinforcement in various animal species (7, 12, 13, 16). Conflicting reports exist as to whether performance of primates in operant tasks modeling learning and short-term memory are impaired by *d*-amphetamine (2, 10, 19), and some reports indicate that *d*-amphetamine improves associative memory (5) and discriminative learning performance (15). However, most of the reported investigations have focused upon *d*-amphetamine's effects on a single behavior rather than upon its effects on several behaviors simultaneously.

We have used a complex operant test battery (OTB) in evaluating the neurobehavioral effects of delta-9-tetrahydrocannabinol, marijuana smoke and other psychoactive drugs (23, 29–31). The present study was one in a series of experiments designed to validate the use of the OTB as a tool in neurobehavioral toxicology. One way to test the validity of the test battery approach is to use relatively well characterized, reversibly acting drugs as reference compounds. Selective behavioral effects of these reference compounds in monkeys can then be compared to their known effects in humans and other animal species. Eventually this data can be used to compare with the effects produced by drugs or environmental toxicants with uncertain mechanisms of action (6). This approach of validating test batteries for use in behavioral toxicology has been discussed more extensively elsewhere (23). Furthermore, Paule *et al.* (21) have used a modified version of this monkey OTB to assess the performance of normal and learning impaired human children thus enhancing the ability to extrapolate from monkeys to humans, an ultimate goal in behavioral toxicology.

The effects of intravenous *d*-amphetamine on a variety of complex operant behaviors in rhesus monkeys were measured here in order to further investigate the utility of this approach. *d*-Amphetamine doses (0.01–1.0 mg/kg) were chosen for study based on literature reports and the criteria that the highest dose

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grossly affected most behavioral endpoints and the lowest dose was without significant effects. The behavioral tasks contained in the battery were delayed matching-to-sample (DMTS), conditioned position responding (CPR), progressive ratio (PR), temporal response differentiation (TRD), and incremental repeated acquisition (IRA). Several reports suggest that *d*-amphetamine affects performance of similar tasks in humans and experimental animals (15, 17, 33, 34). *d*-Amphetamine was chosen for study here because of its reversibility of effect after acute administration and its relatively well characterized mechanism of action (20,24) allowing it to serve as a prototypic sympathomimetic.

METHOD

Subjects

Nine male rhesus monkeys (*Macaca mulatta*) between three and six years of age (10–20% of maximal achievable lifespan) and weighing from four to nine kilograms at the beginning of the study served as subjects. All animals had been previously trained under the schedules in the test battery for approximately two years and had been used in previous studies of acute marijuana smoke, THC, and diazepam administration (29–31). During this study, all nine animals exhibited stable (less than 15% variability over one month) preexposure baselines for the IRA schedule, eight animals for the PR schedule, seven for the CPR schedule, six for the DMTS schedule and four for the TRD schedule. Animal housing, feeding, etc., were as described previously (29).

Apparatus

The apparatus have been described in detail elsewhere (29) and consisted of portable restraint chairs, sound-attenuated behavioral chambers, operant panels and computer consoles. The operant panel was equipped with three press plates that had to be pushed to effect a switch closure and four retractable levers that operated a switch when depressed. The press plates and levers were aligned horizontally with the press plates above the levers. A trough for reinforcer (banana flavored pellet) delivery was located below the levers.

Operant Schedules

The use and description of the operant tasks contained in the primate behavioral test battery have been reported in detail elsewhere (22,29). A brief description follows.

Delayed matching-to-sample (DMTS). For the DMTS task only the press-plate manipulanda were used. At the start of each trial, one of seven white on black geometric symbols, the sample, was projected onto the center plate (side plates were dark). The subject was required to initiate the trial by making an observing response to the center plate. After the observing response was made, the center plate was extinguished for one of six time delays presented pseudorandomly. After the various time delays, all three plates were illuminated, each with a different geometric symbol, only one of which matched the sample. A response to the "match" then resulted in reinforcer delivery, whereas nonmatching responses were followed by a 10-second time-out period (all plates darkened) and then initiation of another trial with either the same or a different sample (pseudorandomly presented). Of the six animals showing stable performance in this task, two were presented time delays of 1, 2, 4, 8, 16 and 32 seconds while the remainder were presented delays of 2, 4, 8, 16, 32 and 48 seconds. Presentation of time delays was based upon individual performance such that individual animal accuracy declined by approximately 20–25% at the longest time delay.

Conditioned position responding (CPR). In the CPR task only the press-plates were used. At the start of a trial, only the center plate was illuminated with either a red, yellow, blue, or green color. Subjects initiated each trial by making an observing response to the center plate, after which it was extinguished and the two side plates were immediately illuminated white. If the center plate color had been either blue or green, responding to the right plate resulted in reinforcer delivery. If the center press plate was illuminated red or yellow, responding to the left plate resulted in reinforcer delivery. Responding at the wrong position initiated a 10-second time-out period followed by initiation of another trial. The sequence of color presentation was yellow, blue, green, red, but the initial color which began each session was randomly presented.

Progressive ratio responding (PR). Animals were required to increase the amount of work (number of lever presses) required for each reinforcer. Only the far right retractable lever (extended) was used in this schedule. Initially, one or two lever presses (depending upon the individual subject) resulted in reinforcer delivery. After each reinforcer was delivered, the response requirement was increased by the initial number of lever presses required for the first reinforcer. The ratios of progression were chosen such that responding generally declined or was abolished (the breakpoint) during each session.

Temporal response differentiation (TRD). For this task, only the far left retractable lever (extended) was used, and the subject was required to hold the lever in the depressed position for a minimum of 10 seconds but no longer than 14 seconds. Releasing the lever too early or too late started another trial.

Incremental repeated acquisition (IRA). The IRA task immediately followed the PR task and required subjects, using all four response levers (extended), to acquire a new sequence of lever presses each test session. IRA began with the presentation of a one-lever response sequence (IRA1). Each response on the correct lever resulted in reinforcer delivery and after 20 correct response sequences (criterion performance), a one-minute time-out period was followed by the presentation of an "incremented" two-lever sequence (IRA2), such that a response on a different lever was required before a response on the original lever produced food. After the 20th errorless two-lever sequence (i.e., no errors were made between the first and last correct lever presses of the required sequence), the task was incremented to a three-lever sequence and so on, up to six-lever sequences.

Procedure

Behavioral sessions were conducted daily, Monday through Friday, and lasted approximately 50 min. Subjects were rotated through our 12 behavior chambers such that no monkey was placed in the same chamber for two consecutive test days in order to avoid disruption of ongoing large-scale chronic behavioral studies. Behavioral schedules alternated daily. For example, progressive ratio (PR 10-min), incremental repeated acquisition (IRA 35-min), and conditioned position responding (CPR 5-min) tasks were presented on one day; the temporal response differentiation (TRD 20-min) and delayed matching-to-sample (DMTS 30-min) tasks were presented the next test day.

Drugs and Dosing Procedure

d-Amphetamine sulfate (National Institute on Drug Abuse, Rockville, MD) was dissolved in sterile bacteriostatic (0.9% benzyl alcohol) saline (Elkins-Sinn Inc., Cherry Hill, NJ) such that the final injection volume was 0.1 ml/kg. The purity of the *d*-amphetamine was determined to be 99.5% by in-house HPLC

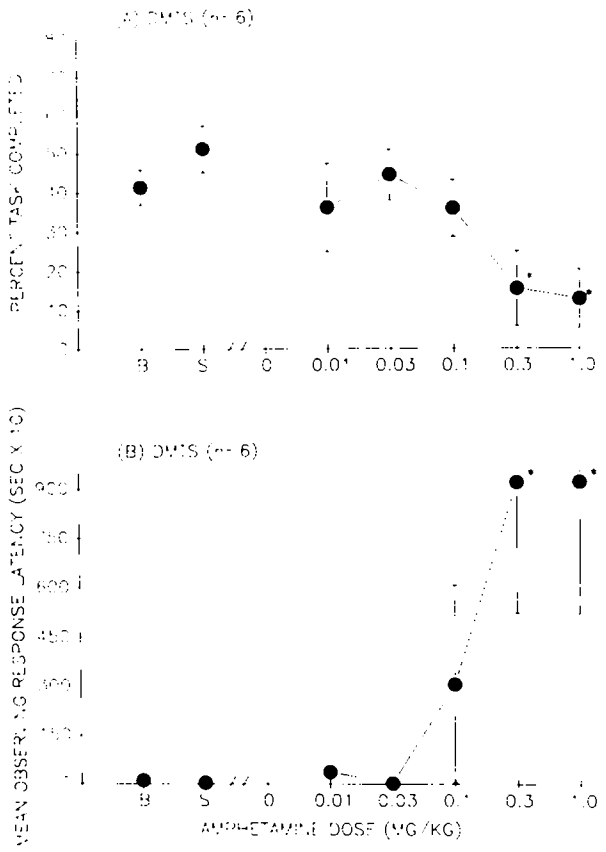

FIG. 1. Effects of *d*-amphetamine on DMTS percent task completed (A) and mean observing response latency (B), n = 6. Each point represent the mean ± SE. On the abscissa, the letter B represent the preexposure baseline of performance and the letter S represents saline control performance determined for five observations. Asterisks represent significant difference from saline controls as determined by Fisher's (LSD) *t*-test ($p<0.05$).

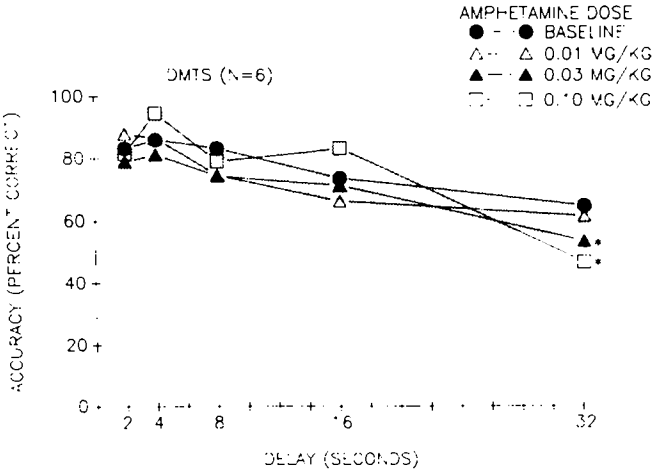

FIG. 2. Effects of *d*-amphetamine on DMTS response accuracy after time delays of 2, 4, 8, 16 and 32 sec. The shaded area represents the ninety-five percent confidence interval constructed from data from five saline control sessions. Each point represents the mean accuracy of five animals. Doses which abolish responding in some animals were omitted. Asterisks represent those means falling outside the ninety-five percent confidence interval.

analysis using a UV detector set at 230 nm. Doses of *d*-amphetamine (0.01, 0.03, 0.10, 0.30 and 1.0 mg/kg, IV) were administered using a minimum number of injections and given in a randomized order to avoid confounding tolerance development. Generally, *d*-amphetamine injections were given on Tuesdays and Fridays while vehicle injections were given on Thursdays. Due to the daily alternation of behavioral tasks, all doses were given twice to provide dose-response data for each set of operant tasks. Approximately 15 min following injections, subjects were placed into operant chambers and behavioral sessions began one min later.

Data Analysis

The endpoints measured in each task have been described in detail elsewhere (29,30). Three fundamental measures are monitored for each test and include percent task completed, response rate or latency, and response accuracy. The percent task completed data are measures of a predetermined criteria of performance (i.e., earning 60 or 120 reinforcers representing performance maximums for the particular task) and are functions of both response rate and response accuracy. Percent task completed is calculated by dividing the total number of reinforcers earned in a given session by the total number of reinforcers possible for a given session and multiplying this quotient by 100. The total number of reinforcers possible for a given task was chosen based upon the length of the test and the task difficulty. The percent task completed endpoint is a convenient and comprehensive measure showing intraanimal stability and is useful for comparing drug effects on performance across tasks (22, 23, 29–31). Since no predetermined criteria of performance exists for the PR task (i.e., each individual determines its own performance maxima) the percent task completed endpoint is not applicable for this task. For the TRD task, mean duration and temporal distribution of lever holds and for the PR task the breakpoint (the magnitude of the last ratio completed for which the animal earned a reinforcer) were also measured.

Statistical Analysis

The overall effect of drug treatments on performance for the various tasks was determined using a one-way repeated measures analysis of variance [ANOVA; (35)]. If overall significance was evident ($p<0.05$), then performance at each dose was compared to vehicle control performance by Fisher's least significant difference (LSD) multiple *t*-tests (18). For DMTS group accuracy data, significance was assigned to those group means falling outside the ninety-five percent confidence intervals constructed from vehicle control observations at each time delay.

RESULTS

Overall Effect of Saline Vehicle

Saline vehicle injections produced no statistically significant group effects on performance in any of the endpoints examined when compared to noninjected baseline data.

Delayed Matching-To-Sample (DMTS)

d-Amphetamine produced dose-dependent decreases in DMTS percent task completed and increases in mean observing response latencies which reached significance following doses of 0.3 and 1.0 mg/kg (Fig. 1). In some animals, increases in mean observing

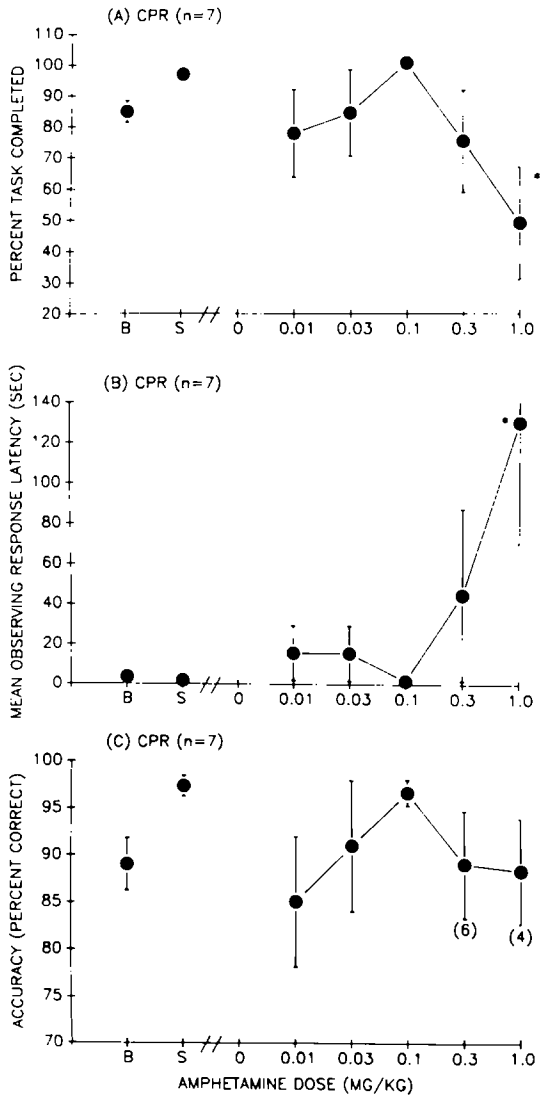

FIG. 3. Effects of *d*-amphetamine on CPR percent task completed (A), mean observing response latency (B) and response accuracy (C), n = 7 unless indicated. Data presented as in Fig. 1.

response latencies occurred at the 0.1 mg/kg dose leading to elevated group means and larger standard errors for this dose. Examination of 95% confidence intervals around saline control response accuracy data for the group (Fig. 2) shows that *d*-amphetamine produced marginally significant decreases in accuracy only at the 32-sec time delay for the 0.03 and 0.10 mg/kg doses.

Conditioned Position Responding (CPR)

d-Amphetamine produced dose-dependent decreases in CPR percent task completed and increases in mean observing response latencies which reached significance at 1.0 mg/kg (Fig. 3). An increase in percent task completed, associated with a decrease in interanimal variability, was evident after vehicle injections (but not statistically significant) and at the 0.1 mg/kg dose when compared to baseline data obtained with no injections. However, variability of saline performance was quite low (SE = 2%), while

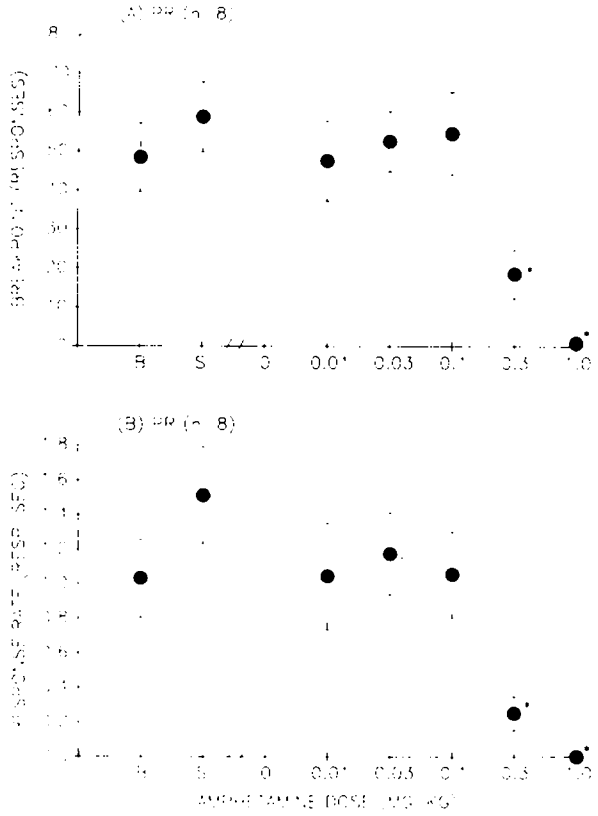

FIG. 4. Effects of *d*-amphetamine on PR breakpoint (A) and response rate (B), n = 8 unless indicated otherwise. Data presented as in Fig. 1.

interanimal variability for the 0.1 mg/kg dose was nonexistent (SD = 0). The accuracy of responding in the CPR test was not significantly affected by *d*-amphetamine (Fig. 3C). When compared to noninjected controls, 0.1 mg/kg *d*-amphetamine and saline injections decreased intersubject variability reflecting the response for percent task completed observed at this dose.

Progressive Ratio (PR)

d-Amphetamine produced significant dose-dependent decreases in PR breakpoint and response rates (Fig. 4) following 0.3 and 1.0 mg/kg. No increases in either of these measures were observed.

Temporal Response Differentiation (TRD)

d-Amphetamine produced significant dose-dependent decreases in TRD percent task completed and response accuracies while having no statistically significant effect on mean response rates (Fig. 5) in part because of the large variability of saline control data. Compared to saline controls, significant decreases were observed in percent task completed following the 0.1, 0.3 and 1.0 mg/kg doses. However, significant decreases in response accuracy were evident at doses of 0.3 and 1.0 mg/kg. As noted for the TRD response accuracy and percent task completed measures, the mean duration (in sec) that the lever was held in the depressed position by the group was also significantly decreased by *d*-amphetamine administration at doses of 0.3 and 1.0 mg/kg (data not shown) thus contributing to the accuracy decreases.

Incremental Repeated Acquisition (IRA)

d-Amphetamine administration produced significant dose-de-

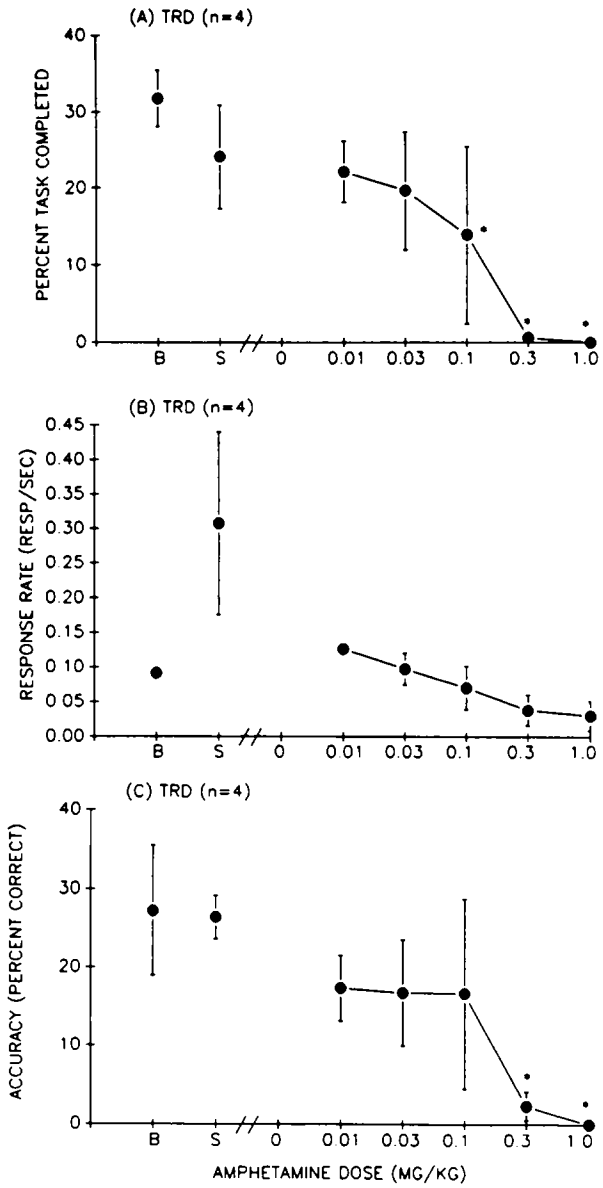

FIG. 5. Effects of *d*-amphetamine on TRD percent task completed (A), mean response rate (B) and response accuracy (C), n = 4. Data presented as described in Fig. 1.

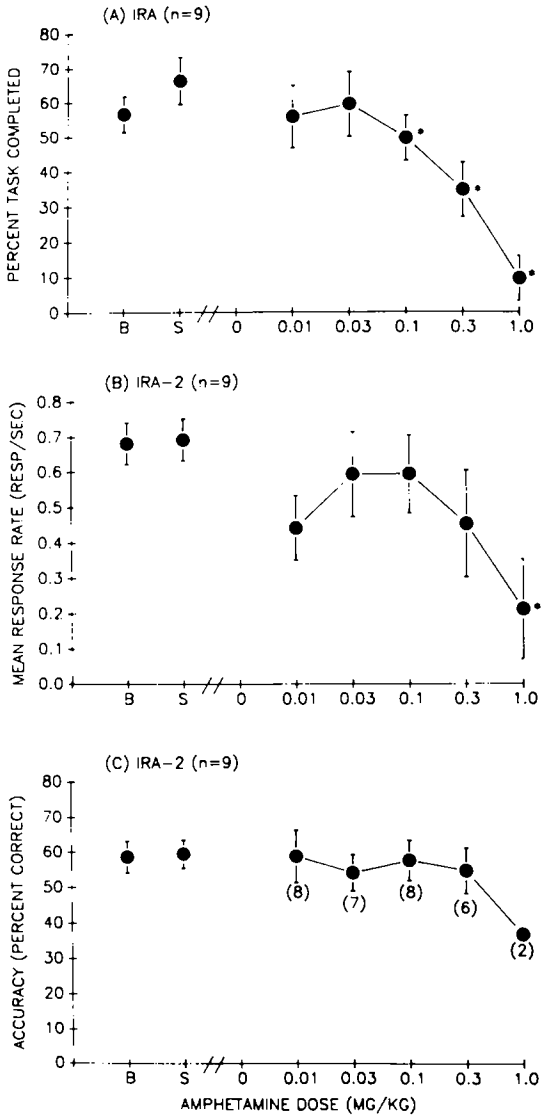

FIG. 6. Effects of *d*-amphetamine on IRA percent task completed (A), response rate (B) and accuracy (C) for IRA2, n = 9 unless indicated otherwise. Data presented as described in Fig. 1.

pendent decreases in IRA percent task completed (Fig. 6A) at the 0.1, 0.3 and 1.0 mg/kg doses. Similarly, dose-dependent decreases in mean response rates for IRA2 (Fig. 6b) and for the IRA1 and IRA3 components (data not shown) were evident but significance occurred only at 1.0 mg/kg dose, while no significant increases or decreases in response accuracy occurred for the IRA2 component (Fig. 6C) or for any other IRA component.

DISCUSSION

d-Amphetamine administration to monkeys selectively altered performance in the behavioral tasks contained in the operant test battery used in this experiment. TRD and IRA percent task completed were decreased significantly at doses of 0.1 mg/kg and above. PR breakpoint and response rate and DMTS response latencies were significantly affected at doses of 0.3 mg/kg and above, while CPR percent task completed and response latencies were only affected at the 1.0 mg/kg dose. In comparison, the effects of delta-9-tetrahydrocannabinol (THC) and diazepam (Valium) in these same animals performing in the same operant test battery (29,30) were quite different. Unlike diazepam and THC, *d*-amphetamine produced significant dose-dependent decrements of response rate and breakpoint in the PR test and delay-dependent decreases in matching accuracy. These observations confirm the notion that complex operant performance is differentially effected by drugs which act through different CNS mechanisms (6).

d-Amphetamine has been reported to produce decreases in matching accuracy in rhesus monkeys (2, 9, 10). In the present study, as in those previously mentioned, we found significant decreases in matching accuracy at the longer 32-sec time delays in the group data. *d*-Amphetamine, at doses that significantly affected matching accuracy, did not significantly affect observing response latencies suggesting a specific effect on matching accu-

racy rather than a general effect on motor function at these doses.

The CPR task was the only task in which a *d*-amphetamine-induced enhancement in performance occurred as indicated by an abolishment of the interanimal variability of the percent task completed measure at the 0.1 mg/kg dose with all seven subjects obtaining a score of 100%. It should be noted, however, that this enhancement did not reach statistical significance using a Fisher's *t*-test. This effect may be similar to that reported by Kulig and Calhoon (15), in which methamphetamine enhanced visual discrimination learning in the marmoset. In contrast, it has been argued that amphetamine, at doses which disrupt performance, affects response control rather than discrimination ability and is consistent with the effects of high *d*-amphetamine doses on CPR performance (25).

The effect of *d*-amphetamine to decrease PR breakpoint and response rate in rhesus monkeys parallels reports of *d*-amphetamine's rate decreasing effects on fixed-ratio performance in pigeons (3), and in rats (16). Similar amphetamine-induced rate decreases have been reported in squirrel monkeys performing under fixed ratio schedules of either food or cocaine reinforcement after doses of 0.3–1.0 mg/kg (11). In contrast, *d*-amphetamine's disruption of TRD performance appears to reflect a general loss of schedule control resulting in decreased lever hold durations. Others have reported similar effects of *d*-amphetamines in pigeons (17), in rats (27), in mice (1) and in rhesus monkeys (8) performing under differential reinforcement of low-rate responding schedules. As in the present study, McMillan and Cambell (17) reported that in pigeons, *d*-amphetamine produced inconsistent changes in response rates with only half of their animals showing an effect. This type of response may explain the lack of statistical significance observed for TRD response rates in this study.

The *d*-amphetamine-induced decrease in the IRA percent task completed was due primarily to decreases in response rates. These data are similar to those obtained by others (19), using repeated acquisition tasks in monkeys. *d*-Amphetamine is reported to selectively disrupt response chain acquisition but not the performance of previously acquired response chains in monkeys performing in repeated acquisition paradigms leading to the overall decline in response rates over the session (32). However, these effects in monkeys differ from those reported in rats where *d*-amphetamine produced response rate increases under a repeated acquisition schedule (28). *d*-Amphetamine (0.1 and 0.3 mg/kg, IP) was also demonstrated to enhance accuracy for 3-lever response sequences in rats performing IRA tasks (22). No such enhancement was seen in this study. The *d*-amphetamine-induced decrease in accuracy noted in rats at doses of 1.0 mg/kg and greater has been attributed to *d*-amphetamine-induced preservative responding (19), an effect produced by high *d*-amphetamine doses (4, 5, 26), but not seen to any great degree in the present study.

The present data indicate that the acute effects of *d*-amphetamine on performance in a battery of complex operant tasks are notably different (decreased response rates in the PR task) than the acute effects of THC or diazepam when given to the same animals performing the same tasks. The ability of compounds such as *d*-amphetamine, diazepam and THC to affect complex performance of one type and not another suggests that responding under the different components of the NCTR operant test battery is subserved, to a great degree, by different CNS processes. The present study suggests that *d*-amphetamine, which facilitates catecholamine neurotransmission, has a more modulatory influence over the networks subserving IRA ("learning") and TRD ("time-perception") responding than over those subserving responding in PR ("motivation") or DMTS ("memory" and "attention") tasks and the least influence over CPR ("color and position discrimination") responding based upon their sensitivity to disruption by *d*-amphetamine. These results exemplify the utility of an operant test battery approach in studying animals exposed to neurotoxic and/or pharmacologic agents since these methods are known to be selectively disrupted by reference compounds affecting different CNS processes. Therefore, this approach can provide behavioral data (i.e., profiles) which may suggest possible mechanisms or brain processes involved in the effects produced from exposure to exogenous compounds.

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REFERENCES

1. Balster, R. L.; Baird, J. B. Effects of phencyclidine, *d*-amphetamine and pentobarbital on spaced responding in mice. Pharmacol. Biochem. Behav. 11:617–623; 1979.
2. Bauer, R. H.; Fuster, J. M. Effects of *d*-amphetamine and prefrontal cortical cooling on delayed matching-to-sample behavior. Pharmacol. Biochem. Behav. 8:243–249; 1978.
3. Branch, M. N. Behavior as a stimulus: Joint effects of *d*-amphetamine and pentobarbital. J. Pharmacol. Exp. Ther. 189:33–41; 1974.
4. Bruto, V.; Kokkinidis, L.; Anisman, H. Attenuation of preservative behavior after repeated amphetamine treatment: Tolerance or attentional deficits? Pharmacol. Biochem. Behav. 19:497–504; 1983.
5. Carr, G. D.; White, N. M. The relationship between stereotypy and memory improvement produced by amphetamine. Psychopharmacology (Berlin) 82:203–209; 1984.
6. Dews, P. B. An overview of behavioral toxicology. In: Weiss, B.; Laties, V. G., eds. Behavioral toxicology. New York: Plenum Press; 1975:439–446.
7. Dews, P. B.; Wenger, G. R. Rate dependency of the behavioral effects of amphetamine. In: Thompson, T.; Dews, P. B., eds. Advances in behavioral pharmacology, vol. 1. New York: Academic Press; 1977:167–227.
8. Fischman, M. W.; Schuster, C. R. Long-term behavioral changes in the rhesus monkey after multiple daily injections of methylamphetamine. J. Pharmacol. Exp. Ther. 201:593–605; 1977.
9. Glick, S. D.; Jarvik, M. E. Amphetamine, scopolamine and chlorpromazine interactions on delayed matching performance in monkeys. Psychopharmacology (Berlin) 16:147–155; 1969.
10. Glick, S. D.; Jarvik, M. E. Impairment by *d*-amphetamine of delayed matching performance in monkeys. J. Pharmacol. Exp. Ther. 169: 1–6; 1969.
11. Gonzalez, F. A.; Goldberg, S. R. Effects of cocaine and d-amphetamine on behavior maintained under various schedules of food presentation in squirrel monkeys. J. Pharmacol. Exp. Ther. 201: 33–42; 1980.
12. Goudie, A. J. Comparative effects of cathinone and amphetamine on fixed-interval operant responding: A rate dependency analysis. Pharmacol. Biochem. Behav. 23:355–365; 1985.
13. Katz, J. L. Second-order schedules of intramuscular cocaine injection in the squirrel monkeys: Comparisons with food presentation and effects of d-amphetamine and promazine. J. Pharmacol. Exp. Ther. 212:404–411; 1980.
14. Katz, J. L.; Barrett, J. E. Effects of *d*-amphetamine and ethanol on responding of squirrel monkeys maintained under fixed-ratio schedule of food presentation and stimulus-shock termination. Pharmacol. Biochem. Behav. 8:35–39; 1978.
15. Kulig, B. M.; Calhoon, W. H. Enhancement of successive discrimination reversal learning by methamphetamine. Psychopharmacologia 27:233–240; 1972.

16. McMillan, D. E. Effects of *d*-amphetamine and caffeine on schedule-controlled and schedule-induced responding. J. Exp. Anal. Behav. 32:445–456; 1979.
17. McMillan, D. E.; Cambell, R. J. Effects of d-amphetamine and chlordiazepoxide on spaced responding in pigeons. J. Exp. Anal. Behav. 14:177–184; 1979.
18. Miller, R. G. Simultaneous statistical inference. New York: McGraw Hill; 1966.
19. Moerschbaecher, J. M.; Thompson, D. M. Effects of phencyclidine, pentobarbital, and d-amphetamine on the acquisition and performance of conditional discrimination in monkeys. Pharmacol. Biochem. Behav. 13:887–894; 1980.
20. Moore, K. E. Amphetamines: biochemical and behavioral actions in animals In: Iversen, L. L.; Iversen, S. D.; Snyder, S. H., Handbook of psychopharmacology. vol. 11. New York: Plenum Press; 1978: 41–98.
21. Paule, M. G.; Cranmer, J. M.; Wilkins, J. D.; Stern, H. P.; Hoffman, E. L. Quantitation of complex brain function in children: Preliminary evaluation using a nonhuman primate behavioral test battery. Neurotoxicology 9(3):367–378; 1988.
22. Paule, M. G.; McMillan, D. E. Incremental repeated acquisition in the rat: Acute effects of drugs. Pharmacol. Biochem. Behav. 21: 431–439; 1984.
23. Paule, M. G.; Schulze, G. E.; Slikker, W., Jr. Complex brain function in monkeys as a baseline for studying the effects of exogenous compounds. Neurotoxicology 9(3):463–472; 1988.
24. Perlow, M. J.; Chiueh, C. C.; Lake, R.; Wyatt, R. J. Increased dopamine and norepinephrine concentrations in primate CSF following amphetamine and phenylethylamine administration. Brain Res. 186:469–473; 1980.
25. Ridley, R. M.; Baker, H. F.; Wright, M. C. Amphetamine disrupts successive but not simultaneous visual discrimination in the monkey. Psychopharmacology (Berlin) 67:241–244; 1980.
26. Ridley, R. M.; Haystead, T. A.; Baker, H. F. An analysis of visual object reversal learning in the marmoset after amphetamine and haloperidol. Pharmacol. Biochem. Behav. 14:345–351; 1981.
27. Sanger, D. J.; Key, M.; Blackman, D. E. Differential effects of chlordiazepoxide and *d*-amphetamine on responding maintained by a DRL schedule of reinforcement. Psychopharmacology (Berlin) 38: 159–171; 1974.
28. Schrot, J.; Boren, J. J.; Moerschbaecher, J. M.; Fontes, J. C. S. Effects of *d*-amphetamine and cocaine on repeated acquisition with time out from avoidance. Pharmacol. Biochem. Behav. 9:659–663; 1978.
29. Schulze, G. E.; McMillan, D. E.; Bailey, J. R.; Scallet, A. C.; Ali, S. F.; Slikker, W., Jr.; Paule, M. G. Acute effects of delta-9-tetrahydrocannabinol (THC) in rhesus monkeys as measured by performance in a battery of complex operant tests. J. Pharmacol. Exp. Ther. 245:178–186; 1988.
30. Schulze, G. E.; McMillan, D. E.; Bailey, J. R.; Scallet, A. C.; Ali, S. F.; Slikker, W., Jr.; Paule, M. G. Acute effects of marijuana smoke in rhesus monkeys as measured by performance in a battery of complex operant tests. Life Sci., in press; 1989.
31. Schulze, G. E.; Slikker, W., Jr.; Paule, M. G. Multiple behavioral effects of diazepam in rhesus monkeys. Pharmacol. Biochem. Behav. 34:29–35; 1989.
32. Thompson, D. M.; Morschbaecher, J. M. Drug effects on repeated acquisition. In: Thompson, T.; Dews, P. B., eds. Advances in behavioral pharmacology. vol. 2. New York: Academic Press; 1979.
33. Weight, M. L.; Ridley, R. M.; Baker, H. F. The effects of amphetamine on delayed response performance in the monkey. Pharmacol. Biochem. Behav. 12:861–864; 1980.
34. Weiss, B.; Laties, V. G. Enhancement of human performance by caffeine and the amphetamines. Pharmacol. Rev. 14:1–36; 1962.
35. Winer, B. J. Statistical principles in experimental design. New York: McGraw Hill, Inc.; 1971:261–305.