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Effects of d-Amphetamine and Cocaine on Repeated Acquisition With Timeout From Avoidance[1]

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SCHROT, J., J. J. BOREN, J. M. MOERSCHBAECHER AND J. C. SIMOES FONTES. *Effects of d-amphetamine and cocaine on repeated acquisition with timeout from avoidance.* PHARMAC. BIOCHEM. BEHAV. 9(5) 659–663, 1978.—The acute effects of d-amphetamine and cocaine on a repeated acquisition baseline with timeout from avoidance were investigated in two rats. Each session the animals acquired one of two different three-member response sequences. Each sequence member was associated with a different response lever. The first two correct responses of each sequence postponed shock for a fixed period of time. The third correct response initiated a signalled timeout (30 sec) from avoidance. Incorrect responses did not postpone shock. The baseline performance was characterized by a decrease in errors within each session, similar to patterns of repeated acquisition maintained by food. In comparison to control sessions, both d-amphetamine and cocaine increased errors and altered the pattern of within-session acquisition. d-Amphetamine increased the rate of sequence completion and the rate of shock delivery in both animals. Cocaine increased the rate of sequence completion in one animal and increased the rate of shock delivery for the other.

Repeated acquisition Avoidance Timeout d-Amphetamine Cocaine Lever-press Rats

THE TECHNIQUE of repeated acquisition has been used to investigate the effects of a number of pharmacological compounds on learning [3, 7, 8, 9, 10, 11, 12]. In these studies behavior was maintained by food reinforcement. For example, in one procedure [7] pigeons were required to learn a different four-member response chain on three keys. Each correct response advanced the chain sequence one member, and each error produced a timeout from reinforcement. In general, it has been found that drugs such as d-amphetamine, cocaine, imipramine, and chlordiazepoxide increase errors and decrease response rate in a dose-related manner.

Recently, a procedure for studying repeated acquisition with avoidance contingencies has been reported [5]. Rats were trained to acquire a different three-member response sequence each session. Each sequence member was associated with a different response lever and auditory stimulus, and the correct sequence of levers changed each session. The first two correct responses of each sequence postponed shock for a fixed period of time, and the third correct response initiated a signalled timeout from avoidance. The animals of that study displayed a biphasic pattern of reacquisition similar to ones displayed for food-maintained responding [1,6]. The pattern was characterized by a progressive increase in accuracy, which stabilized during the last half of the session. Shock density was relatively high at the beginning of each session and declined abruptly as acquisition progressed. The present study was designed to investigate the effects of d-amphetamine and cocaine on this baseline.

METHOD

Animals

Two male Long-Evans hooded rats with a previous history on repeated acquisition with timeout from avoidance served. The animals were maintained at 80% (range, 370–400 g) of their free-feeding body weights throughout the study by regulated post-session feeding. Water was available continuously in the home cage. The animals were individually housed in a temperature-controlled room with a 12 hr light-dark cycle.

[1]The experiments reported herein were conducted according to the principles set forth in the *Guide for the Care and Use of Laboratory Animals*. Institute of Laboratory Resources, National Research Council, DHEW, Pub. No. (NIH) 74–23. This research was supported by NIMH Grant MH 20785 to John J. Boren.

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Apparatus

Two identical test chambers were modified to contain three levers mounted 9 cm apart, center to center, along the rear wall. The levers were located 5 cm above the grid floor and required a minimum force of 0.22 N to operate. Two stainless-steel partitions (each 25×5×0.15 cm), protruded 5 cm into the chamber and separated the three levers. The partitions prevented an animal from operating more than one lever simultaneously. A houselight and a speaker were located on the front wall. The test chambers were housed in larger, sound-resistant chambers equipped with blowers for ventilation. Grid shock was provided by two constant-current shock-generator scramblers that were located in an adjacent room along with solid-state programming modules and cumulative recorders.

Procedure

The rats were trained to press each of the three levers in a particular three-member sequence (cf. [5]). Two different sequences (e.g., 2–3–1 or 1–3–2) scheduled on alternate days were used with each rat. The baseline procedure operated as follows. The beginning of each session was signalled by the illumination of the houselight and onset of auditory clicks (five per second). Shock (1.5 mA, 0.5 sec) was delivered at 10-sec intervals as long as the animal either responded incorrectly (error) or did not respond at all. The first correct response simultaneously reset the shock cycle, advanced the sequence to the second member, and increased the click frequency (25 per sec). The second correct response advanced the sequence, reset the shock cycle, and further increased the click rate (50 per sec). The third correct response produced a timeout of 30 sec, during which all stimuli were off. Termination of timeout returned the sequence to the first member and the procedure recycled until the session ended. Sessions were 100 sequences in duration and were conducted 6 days each week.

When the baseline error and sequence completion rates had stabilized (60 sessions), the effects of cocaine hydrochloride and d-amphetamine sulphate were tested. The salts of both drugs were dissolved in saline solution and injected intraperitoneally 5 min before the start of the session. Drug tests were conducted with the same response sequence and separated by at least two days. Saline administrations of 0.5 cc were given under the same conditions as drug administrations.

Six doses of cocaine, ranging from 5 to 30 mg/kg, and six doses of d-amphetamine, ranging from 0.25 to 4 mg/kg, were administered. The doses of each drug were tested in a mixed order, and a minimum of two determinations were obtained for each dose with each rat. The data for each rat were analyzed by comparing a given drug session with two saline sessions and all of the test-sequence baseline sessions that occurred during drug testing.

RESULTS

The effects of d-amphetamine on three measures of session performance are depicted in Fig. 1. Total errors per session for both subjects are presented in the top of this figure. The highest dose (4 mg/kg) produced consistent increases in error responding in both animals. The majority of the lower dose values produced error levels that were either within or inconsistent with respect to the control range. Two

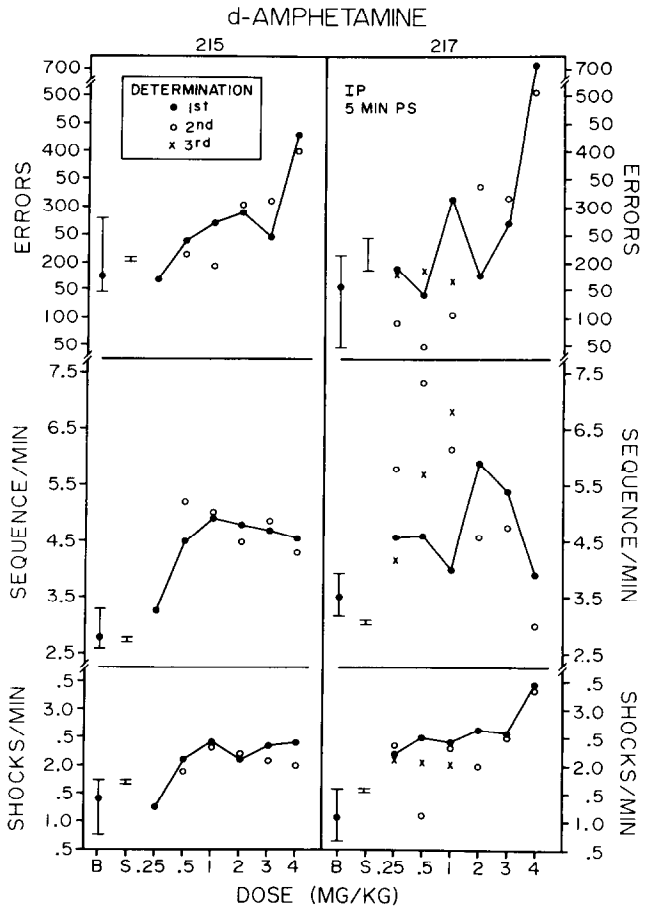

FIG. 1. Total errors, rate of sequence completion, and rate of shock delivery as a function of d-amphetamine dose are shown. The solid circle, open circle, and X represent the first, second, and third determinations at each dose, respectively. The barred lines represent the range of baseline and saline sessions, the solid circle within the baseline range is the median of 9 and 17 sessions for Animals 215 and 217, respectively.

exceptions at doses below 4 mg/kg were found: Rat 215 at 2 mg/kg and Rat 217 at 3 mg/kg showed slight increases in error responding that were consistently outside of the control range.

The middle panel of Fig. 1 presents the data for rate of sequence completion, obtained by dividing avoidance time (session time minus timeout time) into the number of completed sequences. Both animals showed an increase in rate of sequence completion, which peaked at intermediate dose values. The peak elevation in completion rate represented about a twofold increase from baseline. With doses greater than 1 mg/kg the rate of sequence completion declined; for Rat 217 the completion rate was within the control range with a dose of 4 mg/kg. The pattern of responding at 4 mg/kg, however, was not similar to control responding.

The bottom panel of Fig. 1 presents the data for shock density, obtained by dividing avoidance time into the number of shocks delivered each session. Shock density was elevated during drug sessions for both animals. The increase for Rat 215 was practically invariant across doses ranging

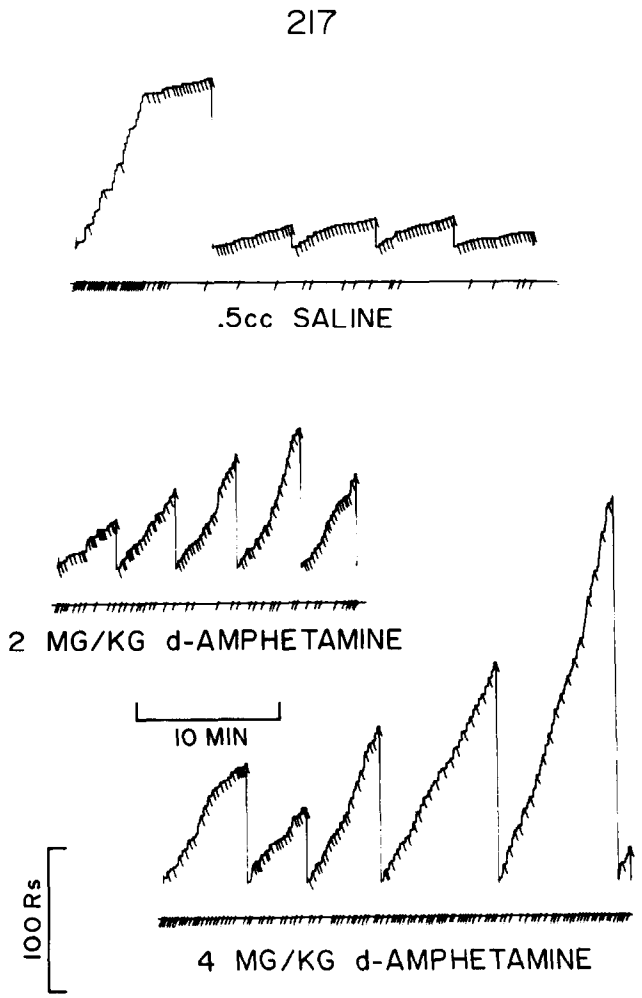

FIG. 2. Cumulative records for Animal 217 showing the effects of d-amphetamine and saline. Incorrect responses stepped the pen, deflections of the response pen indicate timeout (i.e., sequence completion), and deflections of the event pen indicate shock.

from 0.5 to 4 mg/kg. Rat 217 showed a slight increasing trend across doses ranging from 0.25 to 3 mg/kg and an abrupt increase at 4 mg/kg.

Cumulative records for a saline and two d-amphetamine sessions for one animal are depicted in Fig. 2. The saline record shows the biphasic nature of within-session acquisition. Responding during initial sequences was characterized by alternating pauses and runs of incorrect responses together with a high shock density; the animal paused through the shock interval and emitted a burst of responses to a single lever following shock delivery. The first response of a burst was occasionally made on a correct lever, which resulted eventually in sequence completion. After a few sequence completions the pattern of responding abruptly changed. The postshock responding disappeared within the first 20 sequence completions and was replaced by single responses to each lever. Pausing was still in evidence but the duration was generally less than the shock interval. The result was an abrupt decline in shock density during the last four segments of the session. The animal paused most often at the beginning of the sequence and subsequently made rapid single responses on each lever until the sequence was completed. This pattern of responding was stable for the duration of the session. Error responding during the second phase occurred at a rate of about one per sequence, and occasionally series of up to five successive errorless sequences were observed. During the session shown at the top of Fig. 2, the animal emitted 188 errors, completed sequences at a rate of 3.02 per min, and received shocks at a rate of 1.54 per min. The animal received 37 shocks during the initial 20 sequences and 15 shocks during the remaining 80 sequences.

Administration of d-amphetamine disrupted the course of repeated acquisition. At a dose of 2 mg/kg (the middle record of Fig. 2), total errors (336) were increased and response runs on incorrect levers were observed throughout the session. Shock density (2.0 per min), however, was only slightly elevated over saline levels, and the shocks were evenly distributed throughout the session. Rate of sequence completion (4.56 per min) was increased over saline rate even though shock density and error responding increased. This probably occurred because the animal paused less during the drug session.

A dose of 4 mg/kg of d-amphetamine, the bottom record of Fig. 2, produced the greatest alterations in responding. Error responding increased; the animal emitted more than three times as many errors (703) as during the saline session. In addition, the pattern of error responding was altered. Error levels increased as the session progressed, and runs on a single lever increased in magnitude. Shock density (3.37 per min) was elevated during this session. The period of high shock rate seen during the initial portion of the saline session characterized the entire drug session. Sequence completion rate (2.98 per min) was comparable to saline. With this dose, as well as with all others, responding during timeout was comparable to saline and baseline, averaging less than one response per timeout.

The effects of cocaine on the three measures of session performance are depicted in Fig. 3. The data points in this figure were calculated in the same manner as those in Fig. 1. Total session errors for both animals are presented in the top panel of this figure. At doses between 10 and 30 mg/kg, session errors for Rat 215 were consistently above the control range. For Rat 217 errors were consistently increased at doses of 15 mg/kg and above. In addition, the error data from 217 tended to increase with dose. A dose of 30 mg/kg cocaine was required to consistently produce error levels for both animals comparable to those found with 4 mg/kg of d-amphetamine.

The rate of sequence completion data are presented in the middle panel of Fig. 3. Rat 215's rate of correct responding was consistently increased at doses of 15 mg/kg and above. Rat 217, however, only exhibited small increases in rate with cocaine; at 20 mg/kg both determinations were barely above the baseline range. The shock-density data are depicted in the lower panel of Fig. 3. For Rat 215 cocaine generally had no effect on shock density. Shock density, however, was increased at each dose for Rat 217. Moreover, the increase in shock density was similar across the dose range.

Cumulative records from a baseline session and two doses of cocaine for Rat 217 are presented in Fig. 4. During the baseline session the animal emitted 178 errors, completed sequences at a rate of 3.50 per min, and received shocks at a rate of 1.37 per min. The animal received 31

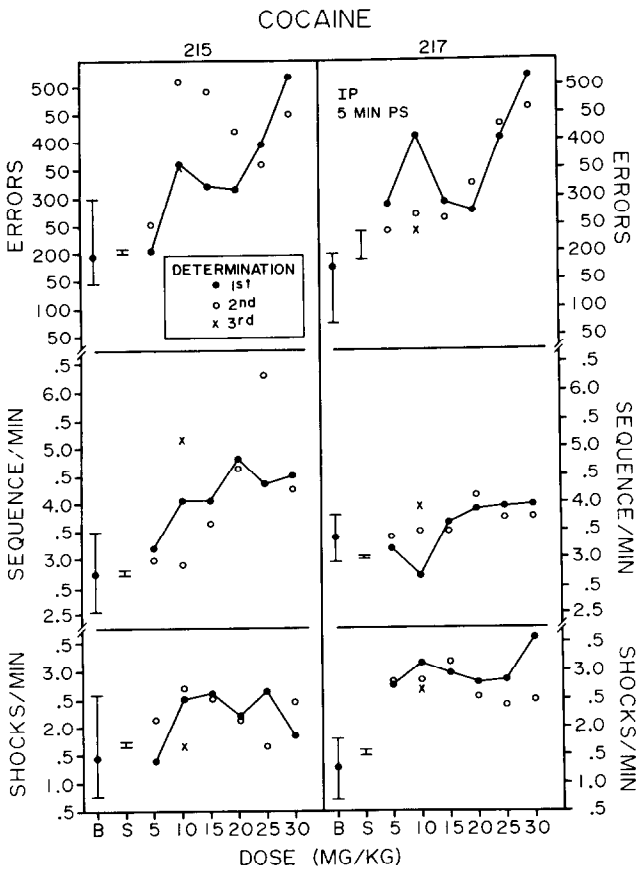

FIG. 3. Total errors, rate of sequence completion, and rate of shock delivery as a function of cocaine dose are shown. The solid circle, open circle, and X represent the first, second, and third determinations at each dose, respectively. The barred lines represent the range of baseline and saline sessions. The solid circle in the baseline range is the median of 12 sessions for both animals.

shocks during the initial 20 sequences and 8 shocks during the remaining 80 sequences.

As illustrated in the middle record of Fig. 4, 10 mg/kg of cocaine produced minimal distortions in the pattern of reacquisition. Errors (269) were elevated, but the biphasic pattern was still in evidence. The pattern of responding during the latter 80 sequences was, however, less consistent than baseline. The animal alternated between short series of near-errorless sequence completions and ones that contained runs of errors. Shock density (2.87 per min) was higher than baseline during this session, primarily because the animal received a greater number of shocks during the last 80 sequences (45) than during the first 20 sequences (37). The sequence completion rate (3.50 per min) with this dose was identical to the baseline rate.

A dose of 30 mg/kg of cocaine (the bottom record of Fig. 4) completely disrupted the pattern of reacquisition. Total session errors (460) were higher than baseline as error responding was increased during each 20-sequence block. Shock density (2.51 per min) and the rate of sequence completion (3.74 per min) were also higher than baseline levels.

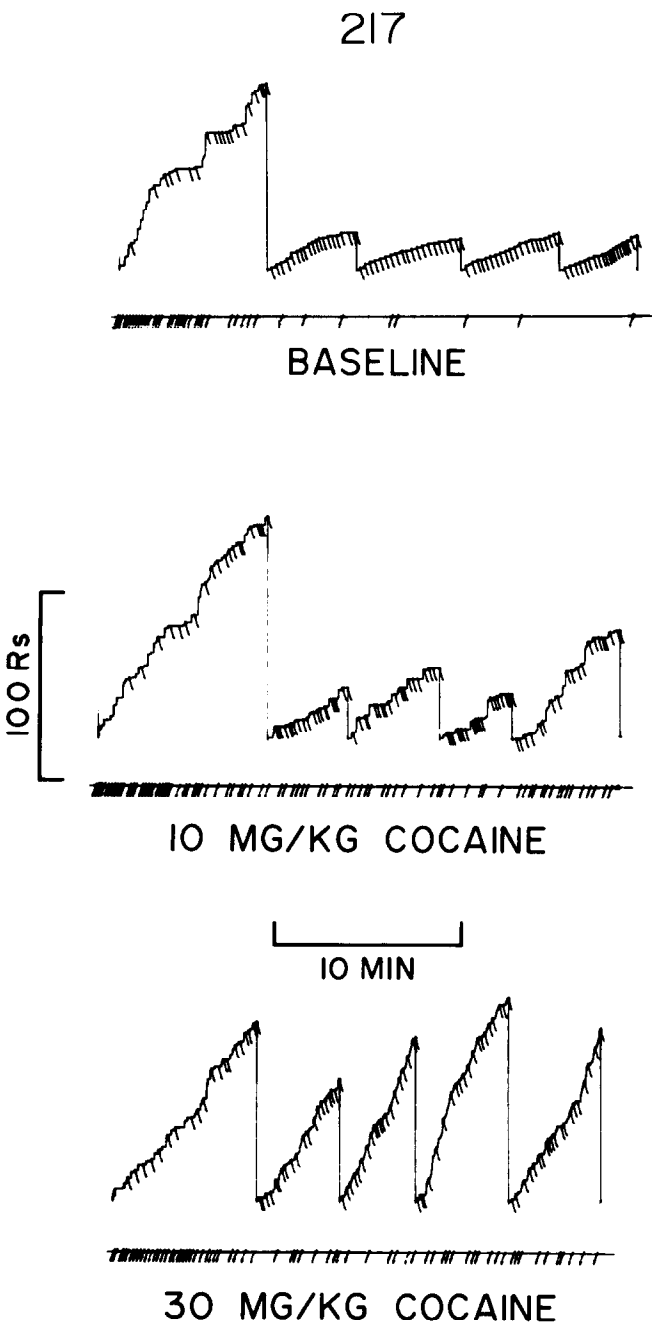

FIG. 4. Cumulative records for Animal 217 showing the effects of cocaine on within-session acquisition. The baseline record was chosen as the best illustration of median repeated acquisition. Recording details are the same as in Fig. 2.

DISCUSSION

These findings indicate that d-amphetamine and cocaine disrupted the normal course of repeated acquisition. The higher doses of both drugs increased errors. This finding is consistent with previously reported data [3, 7, 11, 12] for both d-amphetamine and cocaine on food-maintained repeated acquisition. In the present study, the biphasic pattern

of repeated acquisition evidenced during baseline and saline sessions was disrupted. With higher doses of both drugs, the consistent patterning of responding, i.e., a short pause followed by a single response (seen during the latter stages of control sessions), disappeared. These drug sessions resembled the transition phase throughout, as irregular runs of error responding alternated with pauses in responding.

The rate of sequence completion (or correct responding) and overall responding (correct plus error) during drug sessions never decreased in comparison to the control range. Previous reports concerning the effects of these drugs on food-maintained repeated acquisition have consistently found a decrease in rate of correct as well as overall responding due to increased pausing [3, 7, 11, 12]. The opposite trends in this study were probably a result of the avoidance contingencies. Pausing for 10 sec resulted in shock delivery that tended to elicit response bursts. In fact, the rate-increasing effects were observed at doses comparable to those reported to increase response rate on Sidman avoidance [2,4]. Shock density increased in this study during drug conditions even though the rate of sequence completion increased. The acquisition contingencies, however, obviated any shock-attenuating effects of increased response rate. So long as the animal responded incorrectly, whatever the rate, shocks were more likely to occur.

Under baseline and saline conditions two processes were probably operating simultaneously. The animal had to learn a different set of discriminations each session, matching sequence position with the correct lever. The correct sequence of lever responses may have come under the control of the auditory stimuli, or the controlling stimuli may have been generated from the animal's own behavior. As acquisition took place behavior changed within the session; response runs gave way to an increased frequency of single responses to a lever. Simultaneously, the shock contingencies were operating. As the animal learned the lever sequence it also became more proficient at spacing correct responses. Successful avoidance required the animal to switch levers after each response and within the constraints of the shock schedule. During the latter portions of the control sessions, the animals met both requirements relatively well. Responding was spaced, discrete, and alternated between levers.

During drug conditions the stable pattern of pausing, responding, and switching levers deteriorated and a new pattern emerged. This was characterized by diminished pausing, response runs on the same lever, and less frequent switching. In this study, where a number of possible controlling stimuli were operating (i.e., auditory, timeout, shock interval, and shock), the requisite behavior for completing sequences—switching levers—probably came under the control of shock.

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