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d-Amphetamine and Fixed-interval Performance: Effects of Establishing the Drug as a Discriminative Stimulus[1]

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POLING, A. AND J. B. APPEL. *d-Amphetamine and fixed-interval performance: Effects of establishing the drug as a discriminative stimulus*. PHARMAC. BIOCHEM. BEHAV. 9(4) 473–476, 1978.—The effects of d-amphetamine were examined as a function of conditioning history. The compound (0.5 mg/kg) (1) increased the response rate of rats under a fixed-interval 60-sec schedule, (2) produced greater increases in responding under the fixed-interval schedule when drug administration had been explicitly paired with a fixed-ratio 20 schedule, and (3) decreased responding under the fixed-interval schedule when the drug had been paired with electric shock punishment. Randomly giving amphetamine before fixed-ratio or punishment sessions did not produce such modifications of drug effects under the fixed-interval schedule. These results, like earlier findings, indicate that drug effects can be modified by conditioning history.

d-Amphetamine Fixed-ratio schedule Fixed-interval schedule Punishment Operant history Rats Lever press

THE BEHAVIORAL effects of most drugs depend upon a variety of factors including dose, response rate, conditions under which behavior is maintained, and the history of the behaving organism. Of these factors, the history of the animal as a determinant of drug effects has been described in the least detail. Barrett [1,2] demonstrated that d-amphetamine could increase or decrease responding suppressed by response-dependent electric shock delivery, depending on whether monkeys were given shock-avoidance histories. A related investigation [12] indicated that the same compound decreased rate of responding under a fixed-interval schedule of food reinforcement when rats had been given a history of responding under a fixed-ratio schedule, but increased responding when the animals were exposed to interresponse-time-greater-than-t schedules. These studies indicate that the conditions to which an animal is exposed before a drug is administered can influence subsequent drug effects.

A somewhat different tact was taken by Turner and Altshuler [11]. These investigators trained rats under a variable-interval schedule of food reinforcement and then exposed them to a procedure in which d-amphetamine injections were explicitly or randomly paired with unavoidable shock. For animals in the explicit pairing group, shocks were delivered only during sessions that were preceded by drug injections. Animals in the random pairing group received the same number of injections and sessions in which shock occurred; however, drug injections did not reliably predict shock sessions. After shock sessions were terminated, d-amphetamine decreased the responding of animals in the explicit pairing group and increased the responding of animals in the random pairing group; the response rates of all animals were increased by the drug prior to sessions in which shock occurred. Turner and Altshuler [11] interpreted these data in terms of conditioned suppression; that is, in the explicitly paired group, the drug suppressed responding because it functioned as a conditioned stimulus that had been paired with an unconditioned stimulus, shock.

It has also been well-established that many drugs can function as discriminative stimuli [7]. For example, if left-lever responses are reinforced following d-amphetamine (1 mg/kg) and right-lever responses are reinforced following saline for several sessions, rats respond on the left lever following d-amphetamine (and related compounds) before the first reinforcer is delivered, or during extinction test sessions [4]. It seems likely that discrimination procedures of this kind, in which drug administration is paired with specific experimental contingencies rather than with specific stimuli (above) could modulate subsequent drug effects. This possibility was examined in the present study by assessing the effects of d-amphetamine on fixed-interval responding under conditions in which the drug had been paired previously with either a fixed-ratio schedule of reinforcement or with punishment.

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METHOD

Animals

Six experimentally-naive adult male Sprague-Dawley rats, maintained at 85% of free-feeding weights, served in the experiment. They were individually housed with free access to water in a room of constant temperature (22–24°C) and humidity (40–50%).

Apparatus

A sound-attenuated operant conditioning chamber (R. Gerbrands Co.) was equipped with a lever and a liquid dipper (0.1 ml volume). A 7 W white house light located in the ceiling of the chamber and a 7 W white light located in the dipper opening supplied constant illumination. An exhaust fan provided both ventilation and masking noise. The dipper, filled with sweetened condensed milk, was presented for 4 sec following designated presses of the lever. A force of approximately 0.2 N was required for lever operation. The chamber floor consisted of 0.2 cm metal grids spaced 0.9 cm apart. Electric shock of specified intensity and duration could be delivered to the grids via an AC shock scrambler (Grason-Stadler, Model 1064). Electromechanical control and recording circuits were located in an adjacent room.

Procedure

Phase 1 training. Initially, each animal was exposed to a fixed-ratio 1 (FR 1) schedule of food reinforcement for 5 sessions. Under this schedule, every lever press was followed by dipper presentation. The FR 1 schedule was then changed to fixed-interval 5-sec (FI 5 sec), which was lengthened across 10 sessions to FI 60 sec. Under the FI 60 sec schedule, dipper presentation followed the first lever press emitted at least 60 sec after the preceding dipper presentation. Animals were exposed to the FI 60 sec schedule for 30 sessions, at which time mean response rates showed no obvious trend for 5 consecutive sessions. Throughout the study, sessions were 20 min in duration and occurred once per day, 5 days per week. Intraperitoneal (IP) injections of isotonic saline (1 ml/kg of body weight) were given 15 min prior to all sessions in which d-amphetamine was not given.

Phase 1 testing. After the 30 sessions of FI 60-sec, the effects of 0.5 mg/kg doses of d-amphetamine on FI performance were determined. d-Amphetamine sulfate was mixed with isotonic saline to a 1 mg/ml injection vol., and was injected IP 15 min prior to experimental sessions. Each animal received the drug on 3 occasions, which were separated by 4 FI 60-sec sessions in which saline alone was injected. This procedure was also followed during Phase 2 and Phase 3 testing.

Phase 2 training. Following the initial drug regimen, all animals were exposed to conditions in which an FR 20 schedule was in effect during some sessions, while an FI 60-sec schedule was in effect during other sessions. These conditions were in effect a total of 63 sessions. For animals E7, E8 and E9, the FR 20 schedule was in effect during 21 sessions each of which was preceded by an injection of 0.5 mg/kg of d-amphetamine, while the FI 60-sec schedule was in effect for 42 sessions each of which was preceded by saline; drug (FR 20) and saline (FI 60-sec) sessions occurred in an irregular temporal sequence. Animals R7, R8 and R9 also were exposed to the FR 20 schedule for 21 sessions and received d-amphetamine (0.5 mg/kg) prior to 21 of the 63 Phase 2 Training sessions. For these animals, however, drug injections did not reliably precede either FR 20 or FI 60-sec sessions. That is, the FR 20 schedule followed 7 of the 21 injections of d-amphetamine (33%) and 14 of the 42 saline injections (33%).

Phase 2 testing. All animals were then exposed to the FI 60-sec schedule for 5 consecutive sessions in which drug was not given, after which the effects of 0.5 mg/kg doses of d-amphetamine on FI 60-sec performance were assessed during 3 sessions as in Phase 1 testing (i.e., drug sessions were separated by 4 control sessions).

Phase 3 training. After this second assessment of the effects of d-amphetamine on FI performance was completed, the animals were given 63 sessions during which responding under the FI 60 sec schedule was sometimes punished by 1.0 mA, 300 msec electric shocks delivered under a variable-interval 5-min (VI 5 min) schedule; that is, response-dependent electric shock was programmed to occur on the average of once every 5 min and the interval between specific shock deliveries ranged from 30 sec to 15 min.

For rats E7, E8 and E9, each of the 21 punishment sessions was preceded by a 0.5 mg/kg injection of d-amphetamine; for rats R7, R8 and R9, punishment sessions followed 7 drug injections and no punishment followed 14 drug injections. Thus, as in the FR condition, d-amphetamine was uniquely associated with a change in environmental contingencies for rats E7, E8 and E9, but was not so associated for rats R7, R8 and R9.

Phase 3 testing. Following exposure to the punishment condition, animals were exposed to the FI 60 sec schedule for 5 consecutive non-drug sessions, after which the effects of 0.5 mg/kg injections of d-amphetamine on FI performance were assessed on 3 occasions as described above.

RESULTS

Table 1 shows the mean response rates obtained during the FI 60 sec baseline sessions when drug was not given during each of the 3 testing phases, while Fig. 1 expresses drug effects under each testing phase as percent of the mean control rate obtained under that testing phase (Table 1).

During Phase 1 Testing (i.e., after initial FI 60 sec training), all animals responded at a relatively low rate (Table 1) which was increased by administration of 0.5 mg/kg doses of d-amphetamine (Fig. 1). Saline response rates during the second testing phase (after FR 20 exposure) were considerably higher than those seen during the first testing phase (Table 1). d-Amphetamine injections (0.5 mg/kg) increased the FI 60 sec responding of rats E7, E8 and E9, for which the drug had been explicitly paired with the FR schedule; the relative magnitude of this increase was greater than that produced by d-amphetamine prior to FR 20 exposure (Fig. 1). The rate of responding under the FI schedule of rats R7, R8 and R9 was also increased by d-amphetamine following FR 20 exposure. However, this increase was typically of lesser relative magnitude than that produced by d-amphetamine prior to FR 20 exposure and less than that evidenced by animals for which d-amphetamine was paired with the FR schedule (Fig. 1).

During Phase 3 testing (following punishment) response rates under the FI 60 sec schedule were generally lower than those obtained following FR 20 exposure. d-Amphetamine (0.5 mg/kg) decreased the FI 60 sec responding of rats for which the drug was paired with punishment (E7, E8, E9) relative to the rates obtained during baseline sessions in which drug was not given; the response rates of rats for

TABLE 1

MEAN RESPONSE RATES OF ALL ANIMALS UNDER THE FI 60-SEC SCHEDULE DURING THE 12 BASELINE SESSIONS WHICH PRECEDED DRUG INJECTION DURING EACH PHASE OF TESTING (4 SESSIONS PRECEDING EACH OF 3 DRUG INJECTIONS). PHASE 1 TESTING WAS PRECEDED BY FI EXPOSURE ALONE, PHASE 2 TESTING WAS PRECEDED BY FI AND FR EXPOSURE, AND PHASE 3 TESTING WAS PRECEDED BY FI AND PUNISHMENT EXPOSURE. THE FIRST FIGURE REPRESENTS MEAN RESPONSES/MINUTE ACROSS SESSIONS WHILE THE FIGURE IN PARENTHESIS IS 1 STANDARD ERROR.

	Animals					
	Paired			Unpaired		
Testing Phase	E7	E8	E9	R7	R8	R9
1	6.6 (0.4)	8.9 (0.9)	10.8 (2.3)	16.4 (2.4)	10.2 (1.2)	5.8 (0.9)
2	17.9 (4.2)	24.3 (6.1)	31.6 (3.9)	49.1 (9.8)	39.4 (6.3)	24.0 (5.0)
3	7.1 (1.0)	13.7 (2.2)	9.9 (0.9)	12.5 (2.3)	14.8 (4.1)	9.2 (1.3)

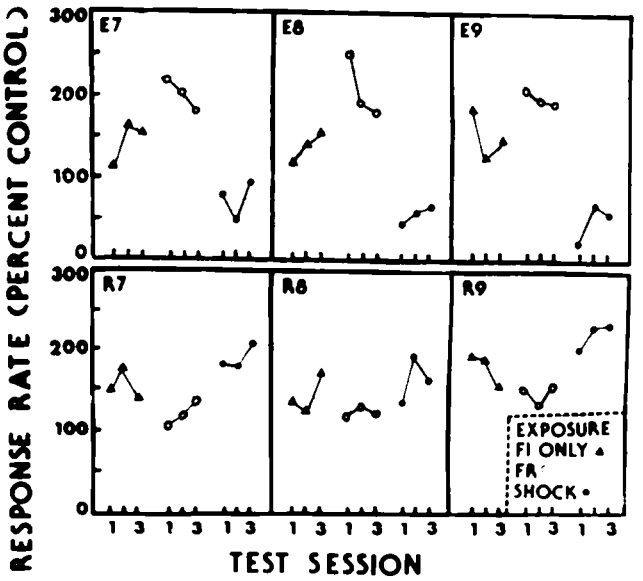

FIG. 1. Response rates under the FI 60-sec schedule during each phase of testing. Each data point represents a single drug injection, expressed as percent of the mean control rate maintained in 12 baseline sessions under that training phase (the 4 sessions which preceded each of the 3 drug injections; see Table 1). Conditons are labelled according to whether an FR 20 schedule or punishment was arranged during the training sessions preceding drug testing. For rats E7, E8 and E9 the FR 20 schedule and punishment were explicitly paired with d-amphetamine injections; for rats R7, R8 and R9, drug injections occurred randomly with respect to the FR schedule or punishment.

which d-amphetamine and punishment were randomly paired (R7, R8, R9) were increased by the drug (Fig. 1).

DISCUSSION

Before animals were exposed to punishment or the fixed-ratio schedule, d-amphetamine increased the low overall rates of responding maintained under the fixed-interval schedule. This is consistent with the results of many studies that have found the drug to increase low and decrease high rates of responding [3, 5, 6, 10].

For animals in which d-amphetamine was not explicitly paired with the FR schedule or with punishment, d-amphetamine also increased responding after exposure to the fixed-ratio 20 schedule and to punishment, although the magnitude of the rate increase produced after fixed-ratio exposure was less than that produced after exposure to the fixed-interval schedule alone. This probably reflects the higher baseline rates maintained after fixed-ratio exposure, since the relative rate-increasing effects of d-amphetamine have been reported to vary inversely with the control (i.e., non-drug) rate of responding [10,12].

For animals in which d-amphetamine was explicitly paired with both FR and punishment schedules, effects depended on conditioning history: the drug increased FI responding after it had been paired with the FR schedule and decreased responding after it had been paired with punishment.

That d-amphetamine could increase or decrease the response rate of an individual animal under the same fixed-interval schedule, depending on experimental conditions with which it had been associated, was the most interesting finding of the present study. This result emphasizes that the behavioral effects of drugs, like those of other stimuli, may depend on the behavioral history of the organism as well as the current environment and the physical (i.e., pharmacological) characteristics of the stimulus. This agrees with the results of previous studies that have demonstrated that conditioning history can influence the effects of drugs on schedule-controlled behavior [1, 2, 11, 12] and can also determine whether a drug serves as a punisher or positive reinforcer [8].

The procedure used in the present study to establish d-amphetamine as a discriminative stimulus (for rats E7, E8 and E9) was similar to that used by Turner and Altshuler [11] to establish the drug as a conditioned stimulus: in both instances, the drug was explicitly paired with specific events. However, in the Turner and Altshuler study, drug administration was paired with forthcoming stimulus events (shock delivery); no response contingency was involved. Thus, a stimulus–stimulus (i.e., drug-shock) pairing had been arranged. In the present study, drug administration was paired

with particular response-consequence relations; d-amphetamine had no predictive value in the absence of responding. Both procedures strongly influenced the behavioral effects of the drug.

Although establishing a psychoactive compound as either a conditioned or a discriminative stimulus can modify subsequent behavioral effects of the drug, the maintenance of such stimulus control depends on continued pairing of the drug with environmental events: if a stimulus is no longer predictive, it eventually fails to control behavior [9]. Neither the present study nor that of Turner and Altshuler [11] specifically examined the duration of alterations in drug effects produced by conditioning history. However, Turner and Altshuler [11] reported that the suppressive effects of pairing d-amphetamine and shock were greatest early in the session and decreased as the number of sessions following the termination of drug-shock pairing increased; a similar effect also occurred in the present study but was not examined systematically.

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