METHYLPHENIDATE AND STIMULUS CONTROL OF AVOIDANCE BEHAVIOR¹

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The introduction of a warning signal that preceded a scheduled shock modified the temporal distribution of free-operant avoidance responses. With response-shock and shock-shock intervals held constant, response rates increased only slightly when the response-signal interval was reduced. The result is consistent with Sidman's (1955) findings under different conditions, but at variance with Ulrich, Holz, and Azrin's (1964) findings under similar conditions. Methylphenidate in graded doses increased response rates, modifying frequency distributions of inter-response times. Drug treatment may have disrupted a "temporal discrimination" formed within the signal-shock interval. More simply, methylphenidate influenced response rates by increasing short response latencies after signal onset; this effect was more prominent than the drug's tendency to increase the frequency of pre-signal responses. When signal-onset preceded shock by 2 sec, individual differences in performance were marked; methylphenidate suppressed responding in one rat as a function of increasing dose levels to a greater degree than in a second animal, but both subjects received more shocks than under control conditions.

Ulrich, Holz, and Azrin (1964) exposed rats to a free-operant avoidance schedule in which the response-shock and shock-shock intervals were held constant throughout but the interval between a response and the onset of an exteroceptive warning signal was systematically varied. Response rates increased when the interval between a response and onset of the warning signal was reduced. More specifically, most avoidance responses occurred shortly after signal onset regardless of the duration of the signal preceding shock; response rate increased greatly when the response-signal interval was reduced to 0.3 sec. The present report describes observations at variance with those of Ulrich *et al.* (1964). Unlike Sidman (1955), Ulrich *et al.* make no mention of a tendency, observed in the present experiment, for avoidance responses to occur in closer temporal proximity to an impending shock than to signal onset.

The present investigation also examined the effects of graded doses of a psychomotor

stimulant, methylphenidate,² on avoidance behavior controlled by a warning signal. Previous experiments have shown that moderate doses of drugs such as *d*-amphetamine (Sidman, 1956; Carlton and Didamo, 1961; Weissman, 1963; Hearst and Whalen, 1963), methamphetamine (Verhave, 1958; 1961), α -pipradrol (Bernstein and Cancro, 1962), and methylphenidate (Stretch, Blackman, and Alexander, 1966) facilitate avoidance behavior by producing overall increases in response rates.

These effects depend partly on the parameters of a given schedule (Bernstein and Cancro, 1962; Stretch *et al.*, 1966, 1967) and partly on shock frequency (Weissman, 1963). Response rates may, however, be reduced by methamphetamine in an animal displaying high rates of responding immediately after shock (Verhave, 1961). Clark and Steele (1963) also found that the characteristic rate-depressant effect of chlorpromazine, when it was administered to rats working on a free-operant avoidance schedule, was not found in one animal which exhibited pronounced, shock-induced bursts of responses under control conditions.

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METHOD

Subjects

Two naive male hooded rats (H1 and H2) of the McGill University-Royal Victoria Hospital strain were approximately three months old at the start of the present work. They had free access to food and water except during experimental sessions.

Apparatus

Avoidance behavior was studied in a Grason-Stadler Type E3125A test chamber contained in a sound-attenuating, ventilated chest. The experimental space measured $9\frac{1}{4}$ by $7\frac{5}{8}$ by $11\frac{1}{2}$ in. Two walls were constructed of sheet metal; the back, top, and door were made of clear plastic. The floor consisted of 18 stainless steel rods on 0.5-in. centers wired to deliver foot shock. A shielded (red) 10-w bulb, which was situated above and to the left of the lever, illuminated the experimental chamber during experimental sessions. A 2-in. wide Gerbrands rat lever was centered on one of the metal walls $3\frac{1}{2}$ in. above the floor and protruded $\frac{5}{8}$ in. into the experimental space.

Experimental conditions were controlled automatically by timers, stepping switches and relays located in an adjacent room. Responses and shocks were tabulated by electromagnetic digital counters and by a Gerbrands cumulative recorder. A Grason-Stadler generator (Type E1064GS), which included a grid scrambler, produced shocks of 0.3-sec duration at an intensity setting of 2.5 ma. White noise, at an intensity of 78 db SPL as measured by a Dawe 1400F sound level meter, served as the warning signal.

Procedure

Experimental sessions lasted 6 hr with at least 18 hr between consecutive sessions; avoidance behavior was studied over a period of six months. Rats H1 and H2 were trained to respond by reinforcing successive approximations to the bar-press. Reinforcement consisted of interrupting, for 15 to 20 sec, shocks which otherwise occurred every 5 sec. When each rat had acquired the response, a free-operant avoidance schedule with a response-shock interval of 20 sec and a shock-shock interval of 5 sec was programmed for 10 sessions (60 hr).

After initial training, the avoidance schedule was modified by including a warning signal for the remainder of the experiment, which consisted of three phases (including drug administration at each stage).

The 20-sec response-shock interval and the 5-sec shock-shock interval were constant throughout the experiment. In the terminology suggested by Ulrich *et al.* (1964), a warning signal (S_1) occurred at a fixed duration after a response and continued until terminated by a response. The time each response delayed the signal is termed the response-signal interval ($R-S_1$ interval) and the time in the absence of a response between onset of the signal (S_1) and delivery of shock (S_2), the S_1-S_2 interval. The avoidance schedule was thus identical to that described by Ulrich *et al.* (1964). Unlike the procedure adopted by Sidman (1955), the warning signal was not terminated by either a response or a shock, whichever came first, but by the response alone.

During the first phase of the experiment, both rats were exposed to the schedule consisting of a 15-sec $R-S_1$ interval and a 5-sec S_1-S_2 interval. Thus, if 15 sec elapsed without a response, the warning signal (S_1) came on and a shock (S_2) was delivered every 5 sec thereafter until a response occurred. When a response was made after signal onset, the signal was terminated, the next scheduled shock (S_2) was postponed for 20 sec (response-shock interval), and signal onset was delayed for 15 sec ($R-S_1$ interval). After 25 sessions (150 hr) under these conditions, drug tests were made. The experimental session was halted momentarily after 2 hr to inject the drug and the session was again interrupted momentarily 2 hr after drug administration to permit counters to be read and reset; *i.e.*, the 6-hr session was divided into three 2-hr periods with an injection being made after the first 2-hr period. Methylphenidate at doses of 2, 4, 8, and 16 mg/kg was injected intraperitoneally (*i.p.*); the effects of each dose were determined in an essentially random sequence on each of three separate occasions with control sessions intervening between drug treatments.

During the second phase, conditions were identical to those of the first except that the response-signal interval ($R-S_1$ interval) was reduced from 15 to 5 sec. After 25 sessions (150 hr) under these conditions, the effects

of methylphenidate at doses of 2, 4, 8, and 16 mg/kg were again determined.

In the final phase, all conditions were identical to those of Phases 1 and 2 except that the response-signal interval (R-S₁ interval) was increased from 5 to 18 sec. After 25 sessions (150 hr), drug tests were made. The effects of methylphenidate at doses of 4, 8, and 16 mg/kg, injected at the beginning of the 6-hr session, were determined. Even though the drug was now administered before a daily session began, the session was twice interrupted momentarily for recording purposes.

RESULTS

Figure 1 shows relative frequency distributions of interresponse times (IRTs) for H1 and H2 during the last session before the warning signal was introduced. When the signal was introduced, lower response rates and consequent changes in the IRT distribution (B and E, respectively) were observed. Although the responses per minute and shocks per hour fluctuated little from session to session, IRT data obtained during the first 25 sessions after the signal was introduced showed

Fig. 1. Relative frequency distributions of IRTs for H1 (upper histograms) and H2 (lower histograms); A and D refer to the last session before the signal was introduced; B and E show the initial effects of signal introduction; C and F refer to performance during the 25th session after introduction of the signal, R-S₁ = 15 sec. White columns indicate responses emitted before signal onset; the black columns indicate responses emitted in the presence of the signal. The last columns (with diagonals) indicate responses emitted after shocks had occurred (S₂-S₂ interval).

that responses tended to occur in closer temporal proximity to an impending shock than to signal onset. The effect is shown clearly in the IRT distributions of Fig. 1 representing the 25th session after signal introduction for each animal (distributions C and F respectively). For example, during the first session with signal present, 53.4% of all responses made by H2 occurred within the first 3 sec after signal onset and only 14.7% occurred in the remaining 2 sec before an impending shock; after 150 hr (25 sessions), however, only 35.5% of all avoidance responses occurred during the first 3 sec, whereas 55.9% were made during the remaining 2 sec after signal onset.

Figures 2 and 3 show how avoidance behavior was affected by methylphenidate. Figure 2 (distributions A-D) refers to performance of H1 under control (A) and three dose levels of methylphenidate (4 mg/kg, B; 8 mg/kg, C; 16 mg/kg, D) when $R-S_1 = 15$ sec. (Data show-

ing the effects of 2 mg/kg methylphenidate are omitted since at this dose no drug effect was clearly discernible, a finding consistent with observations of Stretch *et al.*, 1966). Similarly, Fig. 3 presents data obtained from H2 under comparable experimental conditions (distributions A-D). In all instances of drug administration, methylphenidate reversed the tendency observed under control conditions for avoidance responses to occur in closer temporal proximity to an impending shock than to signal onset. The drug at 8 mg/kg and at 16 mg/kg increased the incidence of responses occurring before signal onset (H1) but did so at all three dosages in the case of H2. Table 1 summarizes the data when $R-S_1 = 15$ sec for both animals under control and drug conditions.

When the $R-S_1$ interval was reduced from 15 to 5 sec during Phase 2, the IRT distributions shown in Fig. 2E (H1) and Fig. 3E (H2)

Fig. 2. Relative frequency distributions of IRTs for H1 during Phase 1 ($R-S_1 = 15$ sec; A-D) and Phase 2 ($R-S_1 = 5$ sec; E-H). Distributions A (control), B, C, and D (methylphenidate at doses of 4, 8, and 16 mg/kg respectively) refer to the first 2-hr period after injection. Similarly, distributions E (control), F, G, and H (methylphenidate at doses of 4, 8, and 16 mg/kg, respectively) refer to the first 2-hr period after injection during Phase 2 when $R-S_1 = 5$ sec.

Fig. 3. Relative frequency distributions of IRTs for H2, plotted in identical fashion to those appearing in Fig. 2, under control (A and E) and drug treatment conditions.

Table 1
Response-Signal Interval = 15 sec.

		Responses/min*		Shocks/hr*	
		Rat H1	Rat H2	Rat H1	Rat H2
Control	1	3.23	3.12	3.5	10.0
	2	3.30	3.23	4.5	6.0
	3	3.43	3.29	7.0	4.0
2 mg/kg	1	3.26	3.23	0.5	11.0
	2	3.56	3.87	2.0	6.5
	3	3.34	3.43	1.5	6.5
4 mg/kg	1	3.33	3.73	0.5	2.0
	2	3.36	3.78	5.0	3.5
	3	3.27	3.46	3.0	7.0
8 mg/kg	1	3.88	5.26	1.0	1.5
	2	3.57	3.75	1.0	2.0
	3	3.53	3.97	1.0	3.5
16 mg/kg	1	3.68	3.53	2.0	8.0
	2	3.66	3.74	8.0	3.0
	3	3.57	3.86	14.5	2.5

*Data obtained during first 2 hr after drug treatment on each of three separate occasions.

were obtained. If, when $R-S_1 = 5$ sec, each signal resulted in an avoidance response with a latency < 1 sec, the rate of responding would be close to 12 per min. However, as may be seen from Table 2, response rates for both animals did not exceed five responses per minute; nor was a rate lower than four responses per minute recorded under control conditions. It is obvious that responses occurred infrequently immediately after signal onset. The IRT distributions (Fig. 2E; Fig. 3E) support this assertion since the modal IRT frequency without exception fell within the limits of 14 ± 2 sec under control conditions; *i.e.*, avoidance responses occurred most frequently 7 to 9 sec after signal onset.

Methylphenidate at doses of 4 mg/kg (F, Fig. 2; F, Fig. 3) 8 mg/kg (G, Fig. 2; G, Fig. 3) and 16 mg/kg (H, Fig. 2; H, Fig. 3) affected the behavior of both animals in a manner consistent with the drug's effects when $R-S_1 = 15$ sec. At 4 mg/kg and 8 mg/kg, responses during the signal tended to occur sooner after signal onset than under control conditions;

for H2 (Fig. 3) more responses tended to occur before signal onset. At 16 mg/kg, responses occurred sooner after signal onset for both animals as compared with control conditions; distribution H, of Fig. 3 reveals a more pronounced effect of the drug in inducing pre-signal responses in one animal (H2) than the other (distribution H Fig. 2).

Table 2
Response-Signal Interval = 5 sec.

		Responses/min*		Shocks/hr*	
		Rat H1	Rat H2	Rat H1	Rat H2
Control	1	4.29	4.18	2.5	4.5
	2	4.01	4.29	5.0	3.5
	3	4.09	4.18	6.0	4.5
2 mg/kg	1	5.28	4.50	1.0	1.5
	2	4.40	5.66	0.0	2.5
	3	4.63	4.20	0.5	3.5
4 mg/kg	1	7.35	7.78	0.5	1.0
	2	6.54	6.33	0.0	2.0
	3	7.60	7.40	0.0	1.0
8 mg/kg	1	8.09	9.63	3.5	0.5
	2	6.79	7.03	0.0	2.5
	3	8.81	6.74	0.0	0.5
16 mg/kg	1	10.45	6.93	0.0	19.5
	2	9.23	5.20	0.5	20.0
	3	10.33	6.47	0.5	4.5

*Data obtained during first 2 hr after drug treatment on each of three separate occasions.

As before, during the third and fourth hours after drug administration, methylphenidate at 4 mg/kg and 8 mg/kg had little apparent effect on behavior; at 16 mg/kg, drug-induced changes in behavior persisted, though to a lesser degree than the effects described above.

During Phase 3, in which R-S₁ was increased from 5 to 18 sec, pronounced individual differences emerged between H1 and H2; Table 3 summarizes the main differences. The higher response and shock rates obtained from H1, as compared with H2, are explained by the fact that whenever H1 failed to avoid a shock, a burst of responses was usually emitted; this difference can be seen from the control records appearing in Fig. 4. Methylphenidate, at doses of 4 mg/kg (A), 8 mg/kg (B) and 16 mg/kg (C) increased the number of shocks received by H1 during the first 2 hr after injection and, at 16 mg/kg, the rate of responding was greatly reduced as compared with control data. Methylphenidate lessened

stimulus control of avoidance responses in H2 by increasing, relative to control conditions, the incidence of pre-signal responses; nevertheless, more shocks were received by this animal at 8 mg/kg (B) and 16 mg/kg (C) than under control conditions or after the lower dosage (A) had been given (Table 3).

Table 3
Response-Signal Interval = 18 sec.

		Responses/min*		Shocks/hr*	
		Rat H1	Rat H2	Rat H1	Rat H2
Control	1	5.25	2.98	58.0	5.5
	2	5.83	2.96	43.0	9.5
	3	6.75	3.05	53.0	11.5
4 mg/kg	1	8.79	4.95	147.0	7.0
	2	5.11	4.01	68.0	17.5
	3	7.38	3.71	123.5	7.0
8 mg/kg	1	7.79	3.64	82.5	57.0
	2	5.59	3.48	63.5	50.5
	3	4.64	3.13	121.0	10.0
16 mg/kg	1	1.85	3.88	364.5	8.0
	2	3.90	3.61	56.5	70.5
	3	3.98	3.83	44.5	5.0

*Data obtained during first 2 hr after drug treatment on each of three separate occasions.

The IRT distributions shown in Fig. 5 further illustrate the differences found between H1 and H2 during Phase 3 under control conditions (A) and the differential effects subsequently observed after drug administration. Whereas methylphenidate reduced stimulus control of avoidance in H2 by increasing the relative frequency of short (pre-signal) IRTs, a higher incidence of post-shock responses can be seen in the distributions describing performance in H1, most noticeably after administration of 16 mg/kg (D).

DISCUSSION

In an experiment concerning discriminated avoidance behavior in rats, Ulrich *et al.* (1964) observed greatly elevated response rates when the response-signal interval was shortened, but the warning signal continued to control responses almost exclusively. The present findings differ from those of Ulrich *et al.* (1964). They stated that the majority of responses "occurred abruptly within the first two class intervals following the onset of the signal" (p. 130). In the present study, responses tended to occur in closer proximity

Fig. 4. Segments of cumulative records showing avoidance behavior ($R-S_1 = 18$ sec) during the first hour after (l to r): a control injection of distilled water, 4 mg/kg (A), 8 mg/kg (B) and 16 mg/kg (C) methylphenidate, respectively. H1 (upper records); H2 (lower records); oblique marks on the record denote shocks.

Fig. 5. Relative distributions of IRTs showing (l to r) control data (A) and the effects of methylphenidate at dosages of 4 mg/kg (B), 8 mg/kg (C) and 16 mg/kg (D) when $R-S_1 = 18$ sec for H1 (upper histograms) and H2 (lower histograms). White columns indicate pre-signal responses; black columns, responses occurring in the presence of the signal. The last columns of each distribution (with diagonals) indicate responses emitted after shocks had occurred (S_2-S_3 interval).

to an impending shock than to signal onset. Sidman (1955) reported comparable data derived under different testing conditions. In his experiment, the signal could be terminated by either a response or a shock, whichever came first; in the present procedure, and in Ulrich's, a response alone terminated the signal, resetting the response-signal interval. Further work is needed to determine the basis for these differing observations.

During the first two phases, methylphenidate consistently modified the temporal distribution of responses in both animals. The drug increased response rates and, as a result, decreased the incidence of longer IRTs, *i.e.* the majority of avoidance responses now occurred sooner after signal onset than under control conditions. Both animals avoided shock more frequently at doses of 4 mg/kg and 8 mg/kg; at 16 mg/kg, however, fewer shocks were avoided than when lower dosages were given. Methylphenidate also increased the incidence of pre-signal responses, but the effect was a less prominent feature of the data than drug-induced changes in the relative frequencies of IRTs after signal onset and was confined largely to the performance of one animal (H2).

Hearst and Whalen (1963), studying the effects of *d*-amphetamine on discriminated-avoidance behavior in rats with a discrete-trials procedure, found that the drug improved performance by increasing the number of shocks avoided. The authors concluded that an explanation which emphasized the disruption of CS-induced "freezing postures" probably best explained their results. The fact that responses occurred in closer proximity to an impending shock than to signal onset in the present experiment could be attributed to signal-induced "freezing" postures, which were subsequently disrupted whenever methylphenidate was administered (Hearst and Whalen, 1963; Kriekhaus, Miller, and Zimmerman, (1965). If, however, the warning signal constituted a relatively aversive stimulus, as this hypothesis implies, a greater incidence of pre-signal responses under control conditions would be expected on the basis of data reported by Sidman and Boren (1957 *a, b*). The Hearst-Whalen hypothesis would also have to account for the fact that when the signal was presented 5 sec before a scheduled shock, avoidance responses under control conditions occurred most frequently

3 sec after signal onset; when the R-S₁ interval = 5 sec, responses occurred most frequently 7 to 9 sec after signal onset. To suggest that signal-induced "freezing postures" persist longer when the signal-shock interval is lengthened may be hard to justify.

Alternatively, methylphenidate could have impaired a "temporal discrimination" formed within the signal-shock interval; this possibility arises from Sidman's (1955) discussion of the properties of warning stimuli in avoidance. However, as Dews and Morse (1961) noted, it is often unnecessary to assume drug-induced disruption of specific timing mechanisms in behavior when results can be more simply explained in terms of an interaction between a drug and the ongoing rate of responding.

More specifically, Dews (1958) has proposed that the behavioral effects of drugs such as the amphetamines are determined largely by the frequency of the response being studied. If the control rate is low, such drugs increase the rate (Sidman, 1956; Morse and Herrnstein, 1956; Schuster and Zimmerman, 1961; Kelleher, Fry, Deegan, and Cook, 1962; Zimmerman and Schuster, 1962; Smith, 1964); but when responses under control conditions occur frequently, amphetamine decreases the overall rate (Owen, 1960; Kelleher *et al.*, 1961; Smith, 1964; Rutledge and Kelleher, 1965). Since many experiments have shown that an important behavioral effect of a drug is to influence the manner in which an animal is affected by shock frequency (Teitelbaum and Derks, 1958; Clark and Steele, 1963; Verhave, 1961; Weissman, 1963) drug-induced changes in avoidance response rates cannot be interpreted solely in terms of a specific rate interaction effect (Cook and Catania, 1964).

Weissman (1963), for example, found that relative and absolute increments in the rate of avoidance responding produced by 1 mg/kg (*i.p.*) of *d*-amphetamine were inversely correlated to a significant degree with baseline shock frequencies, but not with control rates of responding. Rats that received the fewest shocks during control sessions were likely to show the largest increments in responding after drug administration.

The present observations, taken in conjunction with those of Weissman (1963), seem to permit the following statement: when avoidance response rates are relatively low,

but accompanied by infrequent shocks, drugs such as methylphenidate or amphetamine increase the rate; however, if a comparable response rate is associated with a greater incidence of shocks, these drugs may reduce or suppress the rate of responding. This suggestion is offered tentatively but may provide a basis for further work. Since methylphenidate did not increase pre-signal responding to the same degree that the drug modified the temporal distribution of responses after signal onset, an additional problem is apparent; *i.e.*, experiments are needed to determine how the inclusion of an exteroceptive warning stimulus affects the sensitivity of avoidance responding to drug-induced changes.

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