SOME EFFECTS OF METHYLPHENIDATE ON STIMULUS CONTROL OF RATIO AVOIDANCE BEHAVIOR IN THE RAT¹

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After exposure to an avoidance schedule which included a warning signal, a rat was placed on a multiple schedule in which the first component was the same as before, *i.e.*, a single response reset the response-shock interval, delaying shock, and the second component differed only in that four bar-presses were required to postpone shock. A fixed ratio requirement of four responses (FR 4) generated behavior resembling a fixed ratio requirement of one response (FR 1) since responding was controlled by the warning signal but more shocks were received. At a dosage of 2 mg/kg, methylphenidate given intraperitoneally decreased shock frequency during FR 4 periods while FR 1 behavior was not affected; at 4 mg/kg, stimulus control of avoidance responding was impaired during both components. Results at 4 mg/kg were partially confirmed by two animals exposed to an FR 4 avoidance schedule which included a warning signal but with different parameters. Response distributions showed that methylphenidate increased response rates in the absence of the warning signal, *i.e.*, stimulus control of ratio-avoidance behavior was impaired although the increased response rates reduced shock frequency. One hour later responses again occurred more frequently during the signal than in its absence but shocks were less frequent than during control (non-drug) periods.

Many experiments, notably the work of Sidman (1953*a*; 1953*b*; 1958; 1962), have demonstrated that avoidance behavior can be conditioned and maintained without use of an exteroceptive warning signal. But including a warning signal in such free-operant avoidance experiments can produce pronounced changes in the temporal distribution of responses (Sidman and Boren, 1957; Ulrich, Holz, and Azrin, 1964). More specifically, avoidance responses become channeled into the period of time occupied by the signal, resulting in a very low response probability in its absence. This effect is observed reliably in spite of the fact that responses preceding the warning signal serve to postpone its onset.

The present paper is concerned with some of the characteristics of avoidance behavior engendered by a multiple schedule in which, for alternating periods, a rat is required to make either one or several bar-presses to terminate a warning signal, thereby avoiding shock. A second aim was to examine in a preliminary way the effects of a psychomotor

stimulant drug, methylphenidate,² on behavior generated by the multiple schedule described above. Several investigations (Sidman, 1956; Verhave, 1958; Hearst and Whalen, 1963) have shown that psychomotor stimulant drugs, such as the amphetamines, facilitate avoidance behavior by producing overall increases in response rates at moderate dosages. But response rates may be reduced by, for example, methamphetamine, in animals that display a high rate of responding immediately after a shock is delivered (Verhave, 1961).

More generally, Dews (1958*a*) has suggested that the effects on operant behavior of the amphetamines are determined largely by how frequently the response being studied occurs. If the control response rate is low, these drugs will increase the rate (Sidman, 1956; Morse and Herrnstein, 1956; Schuster and Zimmerman, 1961; Kelleher, Fry, Deegan, and Cook, 1961; Zimmerman and Schuster, 1962; Smith, 1964). By contrast, if behavior under control conditions occurs relatively frequently (Dews, 1958*b*; Owen, 1960; Kelleher *et al.*, 1961; Smith, 1964) the amphetamines will decrease the overall rate of responding.

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The present experiments do not permit any definitive conclusion with respect to the generalization proposed by Dews (1958a). But the results do show that ratio-avoidance behavior under some conditions is differentially sensitive to the effects of methylphenidate as compared with the lower rate of responding engendered by a second component of the multiple avoidance schedule.

METHOD

Subjects

A naive, brown hooded female rat (DA1), approximately 200 days old at the start of the experiment, was the principal subject. Two naive, albino female rats (DA2 and DA3) were also used in a modified replication of the main results. All had free access to food and water except during experimental sessions. Rat DA1 was tested daily in 200-min sessions for a period of three months.

Apparatus

Avoidance behavior was studied in a commercially-manufactured test chamber (Grason-Stadler) situated within a sound-attenuating, ventilated chest. Experimental contingencies were controlled automatically by electronic timers, stepping switches, and relays; responses were tabulated by a print-out counter and a Gerbrands cumulative recorder. A Grason-Stadler generator (E1064GS), which included a grid-scrambler, produced shocks of 0.3-sec duration at an intensity of 2 ma.

Procedure

Rat DA1 was trained initially to respond by reinforcing successive approximations to the bar-press. Reinforcement consisted of interrupting for 15-20 sec shocks which otherwise occurred every 5 sec. When DA1 had acquired the response, an avoidance schedule which included a warning signal (white-noise at an intensity of 75 db *s.p.l.* as measured by a Dawe 1400D sound level meter), was introduced. The conditions were such that, in the terminology employed by Ulrich *et al.* (1964), a warning signal (S_1) occurred at a fixed duration after a response (the $R-S_1$ interval). The signal continued until terminated by a response. The time each response delayed the warning signal is termed the $R-S_1$ interval and the time intervening, in the absence of a

response, between onset of the signal (S_1) and delivery of a shock (S_2) is termed the S_1-S_2 interval.

Throughout the experiment, Rat DA1 was exposed to a schedule consisting of an $R-S_1$ interval of 15 sec and an S_1-S_2 interval of 5 sec. Thus, if the rat permitted 15 sec to elapse without a response, the warning signal (S_1) came on and a shock (S_2) was delivered every 5 sec thereafter until a response was made; whenever a response occurred, the next onset of the signal was delayed for 15 sec (the $R-S_1$ interval). The avoidance schedule was identical, therefore, to the contingency described by Ulrich *et al.* (1964). Unlike the procedure adopted earlier by Sidman and Boren (1957), the warning signal (S_1) was not terminated by either a response or a shock, whichever came first, but by the response alone.

After DA1 had spent 25-30 hr under the above conditions, a multiple avoidance schedule was introduced under the following conditions. The experimental session was now divided into eight 25-min periods. During periods 1, 3, 5, and 7, the test chamber was illuminated by a red light and the subject was required to emit one bar-press (FR 1), as before, to terminate the warning signal (S_1) and avoid shock (S_2). During periods 2, 4, 6, and 8, a white light illuminated the experimental space and the rat was required to emit two bar-presses (FR 2) to terminate S_1 . This procedure was operative for five sessions. The ratio requirement for avoidance on the second component was then increased to four responses (FR 4) for the remainder of the experiment (61 sessions). Each shock reset to zero the ratio stepper during the FR 4 components, thus preventing the rat from accumulating responses between successive shocks, *i.e.*, when the animal failed to make the four bar-presses necessary to meet the ratio requirement for avoidance. Either the first or fourth response (FR 1 and FR 4 components, respectively) before onset of the warning signal could reset the $R-S_1$ interval, thus delaying onset of the signal.

The multiple FR 1:FR 4 schedule described above, with $R-S_1 = 15$ sec and $S_1-S_2 = 5$ sec was operative for the remainder of the experiment. Drug tests were not begun until DA1 had been exposed to the multiple schedule for 85 hr. Methylphenidate, at a dosage of 2 mg/kg was injected intraperitoneally 1 min

before a given session began; six administrations at this dosage were given, each of these sessions being separated from the next by two non-drug sessions. Five administrations at a dosage of 4 mg/kg were then given, each separated from the next by three non-drug sessions. Control injections of distilled water were given before non-drug sessions but did not influence behavior measurably.

RESULTS

During the first phase of the experiment, before the multiple schedule was introduced, avoidance responses soon occurred predominantly during the warning signal with a low rate of emission in its absence. Shocks occurred infrequently and "warm-up" periods characteristic of avoidance behavior when no exteroceptive warning signal is present were almost totally absent. The cumulative records appearing on the left of Fig. 1 (*A*, *C*, *E*) typically describe FR 1 behavior before introduction of the multiple schedule; the data in Fig. 2 and 3 also illustrate the stability of response rates and the low incidence of shocks engendered by the FR 1 condition throughout the experiment. The results during the first phase of the experiment were consistent, therefore, with those of Ulrich *et al.* (1964).

Figure 1 shows some of the characteristics of the development of ratio-avoidance behavior generated by the multiple schedule. The upper part of Fig. 1 (*A*:FR 1 and *B*:FR 2) contains two typical segments of the multiple schedule during the session preceding introduction of the FR 4 requirement. Record *B* shows behavior produced by FR 2. It is apparent that some bar-pressing occurred during the warning signal, as evidenced by the step-like character of parts of the record; even so, the rat failed to avoid many of the scheduled shocks and the graph reveals several instances of shock-induced bursts of bar-pressing. The center records (*C*:FR 1 and *D*:FR 4) of Fig. 1 refer to the first session in which the FR 4 avoidance requirement was introduced. Although the response rate is appreciably higher (*D*) than the FR 2 rate (*B*), the rat failed to avoid shock except on three occasions, the last of which was characterized by a sustained high-rate of bar-pressing. Introducing the ratio requirement (*B*, *D*, *F*) during alternate peri-

ods of 25 min did not impair or modify avoidance responding generated by the FR 1 component of the schedule (*A*, *C*, *E*). The lower records of Fig. 1 (*E*:FR 1 and *F*:FR 4) demonstrate the extent to which ratio-avoidance behavior improved in efficiency after 25-30 hr. Although the rat failed to avoid many scheduled shocks during the FR 4 component, and the record (*F*) reveals a tendency for responses to occur in the absence of the warning signal, there is a brief period in which the step-like character of the graph reflects a tendency to

Fig. 1. Segments of cumulative records showing early performance on the multiple avoidance schedule, Rat DA1. Oblique pips denote shocks. *A* and *B*: final session of mult FR 1:FR 2; *C* and *D*: first experimental session in which the ratio-requirement of four responses (*D*:FR 4) was made operative; *E* and *F*: performance after 20-25 hr of exposure to mult FR 1:FR 4 avoidance. Records on the left (*A*, *C*, *E*) describe FR 1 performance in each case; records on the right (*B*, *D*, *F*) denote the ratio component of the schedule. *N. B.*: Figure 4 (*A* and *B*) shows stable performance on the mult FR 1:FR 4 avoidance schedule after 85 hr.

respond after S_1 onset. This tendency for ratio-avoidance responses to be channeled into the S_1 - S_2 interval increased during subsequent sessions, being especially evident towards the end of any particular daily session (see inset cumulative record, Fig. 4, sector B).

A total of 61 sessions were given in which the FR 4 requirement for avoidance operated as the second component of the multiple schedule. Figure 2 plots the average response rate-per-minute for each of these sessions and for both components of the schedule, including rates of responding recorded under drug conditions. These data show, in general, the overall stability of the response rate engendered by the FR 1 component as compared with the FR 4 rates of responding. Methylphenidate, at a dosage of 2 mg/kg, did not influence the rate of responding during FR 1 components of the schedule but the data pertaining to FR 4 components indicate that, at this dosage, the drug consistently reduced the number of responses per minute. At 4 mg/kg, there is some evidence that methylphenidate increased the FR 1 response rate while con-

tinuing, in general, to reduce the response rate produced by the FR 4 condition, although the latter effect is not as clear as at the dosage of 2 mg/kg.

Figure 3 plots the average number of shocks delivered during 25-min periods of the multiple schedule for the 61 sessions shown in Fig. 2. Shock frequency during FR 1 periods was extremely low throughout and was not affected by methylphenidate. On the other hand, shocks occurred frequently during the second component, especially during the first 10 sessions in which FR 4 was effective. Thereafter, the incidence of shocks decreased and was subsequently reduced further whenever methylphenidate was administered.

From Fig. 2 and 3 it is evident that avoidance behavior engendered by FR 1 components was relatively insensitive to the effects of methylphenidate described in terms of the average response rate-per-minute and shock frequency, respectively. However, the drug was found to decrease response rates produced by the FR 4 requirement for avoidance and, at the same time, decreased the incidence of

Fig. 2. Mean response rate-per-minute for 61 consecutive daily sessions of mult FR 1:FR 4 avoidance, showing control (●) and drug (○) data, Rat DA1. The first six open (○) circles refer to the effects of methylphenidate at a dosage of 2 mg/kg while the remaining five show the effects of the drug at a dosage of 4 mg/kg.

Fig. 3. Average numbers of shocks occurring during 25-min periods of the mult FR 1:FR 4 avoidance schedule for 61 consecutive sessions. Open circles (O) describe the effects of methylphenidate at two dosages, plotted in an identical manner to Fig. 2; closed circles (●) denote control (non-drug) data.

shocks, thus exerting a differential and facilitatory effect on behavior generated by one of the components of the schedule.

The data in Fig. 2 and 3 are perhaps better illustrated by the cumulative records in Fig. 4. The upper records (*A* and *B*) are typical of a non-drug session and improved efficiency of ratio avoidance behavior (*B*), defined in terms of a lower incidence of shocks as the session proceeds, is clearly evident. The step-like nature of these records (see inset) denotes emission of responses within the S_1 - S_2 interval and a lack of bar-pressing in the absence of the warning signal.

The center records of Fig. 4 (*C* and *D*) illustrate the effects of methylphenidate at a dosage of 2 mg/kg. While responding generated by FR 1 components of the session (*C*) remains unaffected by the drug, the incidence of shocks delivered during FR 4 components (*D*) is appreciably reduced as compared with the control condition (*B*), although the warning signal continues to control behavior. There is a tendency for shocks to begin to recur during the final FR 4 period.

The lower records (*E* and *F*) describe the effects of the drug at a dosage of 4 mg/kg. In

some respects they resemble those at 2 mg/kg. There is some evidence of bar-pressing, however, in the absence of the warning signal on both FR 1 and FR 4 components and, in addition, the early warm-up effects associated with the onset of FR 4 periods (see sectors *B* and *D*) are eliminated at this dosage.

Figure 5 describes the effects of methylphenidate on behavior generated by an FR 4 schedule of avoidance in two additional animals designated DA2 and DA3, respectively. These rats were subjected daily for 4 hr to an avoidance schedule beginning with FR 1 (10 sessions), followed by FR 2 and FR 3 (five sessions each) and, finally, FR 4 avoidance. After approximately 60-hr exposure to the FR 4 condition, drug tests were made. For Rat DA2, the R - S_1 interval = 20 sec and the S_1 - S_2 = 5 sec. For Rat DA3, R - S_1 = 5 sec, S_1 - S_2 = 5 sec.

The data shown in Fig. 5 refer to a typical avoidance session for each animal in which the session was halted momentarily to permit an intraperitoneal injection of methylphenidate at a dosage of 4 mg/kg. The cumulative records (*A* and *D*) represent control data, and it is clearly apparent that response rates differed appreciably for the two animals. These reflect

Fig. 4. Cumulative records showing the effects of methylphenidate on mult FR 1:FR 4 avoidance behavior, Rat DA1. The records refer to three complete sessions of 200-min duration, 25-min periods of FR 1 (1, 3, 5, 7, on the left) being alternated with 25-min periods of FR 4 (2, 4, 6, 8, on the right) in each case. Thus, *A* (FR 1) and *B* (FR 4) describe behavior as it occurred during a non-drug (Control) session; *C* and *D* refer to a single session in which the effects of methylphenidate at a dosage of 2 mg/kg were tested; *E* and *F* show the effects of the drug at 4 mg/kg. Oblique pips denote shocks; insets illustrate the manner in which ratio-avoidance responses occurred within the S_1 - S_2 interval.

the different schedule parameters employed in each case (average response rates per minute³ were 11.10 and 43.20 for rats DA2 and DA3, respectively).

Drug injections were made after 2 hr (arrows) and the effect, in both cases, was to increase substantially the rate of lever-pressing (*B* and *E*). However, 1 hr after drug adminis-

tration (*C* and *F*) bar-pressing occurred again predominantly within the S_1 - S_2 interval (see insets) but the incidence of shocks remained below control rates.

The data shown as cumulative records in Fig. 5 are perhaps better illustrated by reference to the response distributions shown in Fig. 6. These distributions were not obtained as conventional interresponse time analyses where each response resets the distribution to the first class interval. Instead, only the

³These data are based on 10 control (non-drug) sessions, each of 4 hr duration.

fourth response to occur within the response-shock ($R-S_2$) interval reset the distribution. Thus, each response was classified as it occurred within the $R-S_2$ cycle, but only the fourth response, which reset the $R-S_1$ interval, simultaneously reset the distribution to the first class interval. If the rat failed to emit four responses (the ratio-requirement for avoidance) before a shock occurred, all subsequent responses appeared in the post-shock class interval, (25 sec + (Rat DA2) and 10 sec + (Rat DA3), respectively), until the ratio requirement for avoidance was attained when the analysis was again reset to the first class interval.

From the modified interresponse time distributions in Fig. 6, it is clear that both subjects, under control conditions (*A* and *D*), emitted ratio-avoidance responses mainly in the presence of the warning signal; however, stimulus control of ratio-avoidance behavior

was impaired soon after injection of methylphenidate (*B* and *E*); i.e., the drug increased the incidence of short interresponse times. This effect was found to be transitory; within 1 hr responses again occurred primarily within the S_1-S_2 interval (*C* and *F*) even though the behavioral effects of the drug, defined in terms of shock elimination, persisted as compared with control conditions.

DISCUSSION

In a recent study of stimulus control of avoidance behavior in rats, Ulrich *et al.* (1964) observed greatly elevated response rates when they reduced the $R-S_1$ interval, although the warning signal (S_1) continued to control responding almost exclusively. The present experiments would appear to demonstrate a second method of increasing response rates in experiments of this type as a result of intro-

Fig. 5. Sample cumulative records describing the effects of methylphenidate, at a dosage of 4 mg/kg, on discriminated ratio-avoidance behavior (FR 4) taken from a single session for Rats DA2 (*A*, *B*, *C*) and DA3 (*D*, *E*, *F*), respectively. Records *A* and *D* describe behavior of each animal before drug administration; *B* and *E* illustrate the initial effects of the drug, administered at arrows; *C* and *F* describe behavior as recorded 1 hr after drug administration; insets show control of ratio-avoidance responding by the warning signal (S_1).

ducing a low-valued fixed ratio requirement for avoidance. The results also indicated that this method does not necessarily impair stimulus control of avoidance responding, although the behavior generated by the FR 4 contingency is appreciably less efficient in terms of eliminating shock than that engendered by FR 1. Thus, responding during both components of the multiple FR 1:FR 4 avoidance schedule was channeled predominantly into the S_1 - S_2 interval. In addition, the initially high incidence of shocks during FR 4 components did not modify in any way the degree of stimulus control exerted by the warning signal or impair the efficiency of avoidance behavior during FR 1 components. More generally, the present observations stress the need for further experiments designed to examine specifically possible interactions between the ratio requirement and schedule parameters, *i.e.*, the R - S_1 and S_1 - S_2 intervals, in terms of the degree of stimulus control exerted by the warning signal and in terms of shock frequency.

Until such experiments have been carried out, no definitive conclusions concerning the effects of methylphenidate on ratio-avoidance behavior can be drawn because the environmental determinants of the behavior in question have yet to be identified and isolated. Some preliminary comments can be made, however, which relate the present observations to previous work in this area.

The present results are not inconsistent with those of several previous experiments in which psychomotor stimulant drugs have been shown to facilitate avoidance behavior studied under conditions which involved either the inclusion (Hearst and Whalen, 1963; Kriekhaus, Miller, and Zimmerman, 1965) or absence (Sidman, 1956; Verhave, 1958) of an exteroceptive warning signal. Verhave (1958), for example, showed that low dosages of methamphetamine facilitated Sidman avoidance behavior in rats by increasing overall response rate, providing the animal displayed some minimum tendency to respond before drug administration. Hearst and Whalen (1963),

Fig. 6. Modified interresponse time distributions, describing the effects of methylphenidate, at a dosage of 4 mg/kg, on the behavior shown as cumulative records in Fig. 5. For explanation of these distributions, see text; white columns denote response percentages in the S_1 - S_2 interval and the final column in each distribution refers to responses occurring after shock (S_2). *A* and *D*: control data, rats DA2 and DA3, respectively; *B* (DA2) and *E* (DA3): effects of drug during period of 1 hr immediately after injection; *C* (DA2) and *F* (DA3): effects of the drug during the second hour after administration.

studying the effects of *d*-amphetamine on discriminated-avoidance performance in rats with a discrete trials procedure, found that the drug significantly improved performance without affecting lever-responding in non-conditioned stimulus periods. The authors suggested that of several possible explanations for the drug's effects, an interpretation which emphasized the disruption of CS-induced "freezing" patterns probably best explained their results.

However, since in the present experiments FR 1 avoidance behavior was found to be characterized by (i) near maximal shock avoidance and (ii) almost exclusive control by the warning signal, it is perhaps not surprising to find that, at a dosage of 2 mg/kg, methylphenidate neither impaired nor facilitated an already stable and efficient pattern of avoidance behavior. When, by contrast, the effects of the drug on behavior produced by the FR 4 requirement for avoidance are considered, it is apparent that the drug at the same dosage exerted a differential and facilitatory effect. More specifically, the relatively low rate of responding during FR 1 components was insensitive to the effects of methylphenidate at 2 mg/kg while the higher response rate engendered by FR 4 components was reduced, an effect accompanied by a decreased incidence of shocks.

At a dosage of 4 mg/kg, methylphenidate tended to increase marginally the rate of responding during FR 1 components (see Fig. 2; also Fig. 4E) while continuing to reduce shock frequency on FR 4 components as compared with the control conditions (see Fig. 3). However, the rate-depressant effect of the drug on ratio-avoidance responding at 2 mg/kg was less clearly discernible at the higher dosage; nor was this consistent with the effects of the drug when administered subsequently to Rats DA2 and DA3 tested under different schedule conditions and parameters than Rat DA1. It is interesting that the rate-enhancing effect of methylphenidate observed when the drug was administered to these two subjects was proportionately greater when the control rate of responding was relatively low (Rat DA2; average response rate/minute = 11.10) than when it was relatively high (Rat DA3; average response rate/minute = 43.20); this finding appears to be in agreement with Dews (1958a) proposal concerning drug-rate inter-

action effects mentioned earlier. Any such conclusion based on the present findings would be premature because the ranges of schedule parameters and of dosages were not sufficiently varied. It has also been shown in at least two recent investigations (Teitelbaum and Derks, 1958; Clark and Steele, 1963) that an important behavioral effect of a drug is to influence the manner in which an animal is affected by shock frequency and the way in which it will work to avoid shock. Since, in the present experiments, shock frequency also may have partially determined the magnitude of the drug's effects, the specific factors responsible for the results cannot, as yet, be identified. Finally, the facilitatory effects of methylphenidate observed in the present experiments were not evident during subsequent (non-drug) sessions; this observation agrees with earlier evidence (Verhave, 1958) that improved avoidance induced by psychomotor stimulant drugs does not transfer to non-drugged states.

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