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Effects of *d*-Amphetamine, Chlordiazepoxide and Promazine on Responding of Squirrel Monkeys Maintained Under Fixed-Interval Schedules of Food Presentation and Stimulus-Shock Termination[1]

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BARRETT, J. E., S. I. DWORKIN AND R. R. ZUCCARELLI. *Effects of d-amphetamine, chlordiazepoxide and promazine on responding of squirrel monkeys maintained under fixed-interval schedules of food presentation and stimulus-shock termination.* PHARMAC. BIOCHEM. BEHAV. 7(6) 529–535, 1977. – Responding of two squirrel monkeys was maintained under a multiple 5-min fixed-interval schedule of food presentation and termination of a stimulus in the presence of which shocks occurred. Under the stimulus-shock termination schedule, shocks occurred independently of responding, on the average of every three minutes; a response after 5 min terminated the prevailing stimulus and shock-presentation schedule. Response rates and patterns of responding under both schedules were comparable although they differed slightly between monkeys. d-Amphetamine increased and promazine decreased responding under both fixed-interval schedules. Chlordiazepoxide increased responding maintained by food presentation but decreased responding maintained by termination of the stimulus-shock complex. Under certain conditions and with certain drugs, the event that maintains responding can determine the effects a drug will have on behavior.

Fixed-interval schedule Food presentation Stimulus-shock termination Escape Drugs d-Amphetamine Chlordiazepoxide Promazine Multiple schedule Squirrel monkey

COMPARISONS of the effects of drugs on behavior maintained by different consequences have been of long-standing interest in behavioral pharmacology [8,14]. Because the effects of drugs often have been shown to depend critically on the rate and pattern of ongoing behavior [5, 7, 9, 14], it has been essential that drug effects on behavior maintained by different events be examined when responding is comparably controlled [19,20]. Kelleher and Morse [13], for example, maintained responding of squirrel monkeys under a multiple fixed-interval fixed-ratio schedule by the termination of a visual stimulus associated with a schedule of shock presentation (see also [18]). Responding maintained by the stimulus-shock termination schedule was comparable to that maintained with other monkeys under an identical schedule of food presentation; i.e., despite the differences in consequent events, patterns of responding were similar whether maintained by food or by the termination of a schedule complex associated with shock. The effects of d-amphetamine and chlorpromazine were independent of the event that maintained responding, but did depend on the schedule under which those events occurred. Other experiments in which responding was maintained by different events have also reported that drugs did not exert differential effects that depended on the type of event that maintained responding [3, 23, 24].

Recent experiments have examined the effects of drugs on behaviors comparably maintained by fixed-interval schedules of food or electric shock presentation. Under these conditions amphetamine [15] and cocaine [1] increased responding under both schedules. Chlorpromazine typically decreased responding, but the decreases at a given dose were greater with shock than with food-maintained responding [15]. Morphine, however, increased responding maintained by shock presentation, but only decreased food-maintained responding [15]. Increases with morphine, methadone, naloxone and nalorphine were also reported when responding was maintained by shock presentation or by the termination of a stimulus-shock complex; these

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drugs only decreased responding that produced food [16]. Differential drug effects on responding maintained by food or shock presentation were also found with ethanol, chlordiazepoxide and pentobarbital; these three drugs decreased responding maintained by shock presentation but increased responding occurring under the schedule of food delivery [1]. Taken together, these findings suggest that there are at least certain conditions under which the effects of drugs depend on the type of event, even when rates and patterns of responding are comparable [17,21].

The present experiment further examines the effects of drugs on behavior comparably maintained by different events. Responding was developed and maintained under a multiple fixed-interval schedule of food delivery and termination of a stimulus in the presence of which shocks occurred. The fixed-interval stimulus-shock termination schedule differed from that used in previous studies where continuous shocks occurred throughout the interval [3], or where shocks were scheduled to occur at the end of the interval [13, 15, 16, 18]. In the study reported here, shocks occurred independently of responding on the average of every 3 min throughout the interval. Rates and patterns of responding under the termination schedule were nearly identical to those maintained by food presentation. Whereas d-amphetamine increased and promazine decreased responding maintained by both events, chlordiazepoxide increased food-maintained responding but decreased responding maintained under the termination schedule.

METHOD

Animals

Two experimentally naive adult squirrel monkeys *(Saimiri sciureus),* one female (MS-28) and one male (MS-30), were maintained at approximately 80% of their free-feeding body weights. Both were housed individually and had unrestricted access to water.

Apparatus

During experimental sessions the individual monkeys were seated in a clear Plexiglas restraining chair [11]. The front wall of the chair was equipped with a response lever (BRS/LVE No. 121-05), a receptacle into which 300 mg Noyes banana flavored food pellets could be delivered (Gerbrands pellet dispenser, Model No. D–1) and a stimulus panel consisting of three pairs of 7.5-W colored lamps. Each depression of the response lever exceeding a force of approximately 20 g (0.196 N) produced the click of a feedback relay mounted behind the front panel and was recorded as a response. Electric shocks were delivered through brass electrodes resting on the shaved portion of the monkey's tail. The tail was held motionless by a small stock. Shock was 650 V a.c., 60 Hz and was approximately 200 msec duration, delivered through series resistance. Electrode paste (EKG Sol) was applied to the shaved area of the tail prior to each session. During the experimental session the chair was enclosed in a sound-attenuating chamber equipped with white noise and an exhaust fan.

Procedure

Both monkeys were trained initially to take available food from the receptacle and to respond to the sound of the pellet dispenser. During lever-press training, each response produced food. The likelihood of lever pressing was increased by attaching a small piece of adhesive tape to the lever so that a portion of the tape extended below the lever. Once lever pressing was occurring at a steady rate, the schedule was changed gradually to a 1-min fixed-interval schedule. Under this condition, the first response after a 1-min period produced food (FI 1-min).

Following approximately two-weeks training under the FI 1-min food-presentation schedule, a second condition was initiated consisting of a one-min period during which shock was delivered on the average of every 90 sec, independently of responding (variable-time or VT 90-sec schedule). The first response after the one-min interval elapsed terminated the lights illuminating the chamber, stopped the tape that arranged the scheduled shocks, and produced a one-min period during which responding had no scheduled consequences (timeout). This stimulus-shock termination schedule alternated regularly with the food presentation schedule. The two components were separated by the 1-min timeout period. During the food-presentation component white lamps were illuminated, whereas red lamps were illuminated during the stimulus-shock termination schedule.

Over a one-week period the interval length in both components was increased to 5 min and the schedule of shock presentation was changed to VT 3-min. During the initial phases shock intensity was 5 mA for both monkeys; manipulations in shock intensity were conducted to produce response rates maintained by stimulus-shock termination that were comparable to those maintained by food. Under the final conditions, shock intensity was 5.0 mA for MS-28 and 1.0 mA for MS-30. Experimental sessions were conducted 5 days per week (Monday through Friday) and consisted of 10 regularly alternating cycles of each component plus timeout.

Drug Procedure

Drugs were first administered after 32 sessions under the multiple 5-min fixed-interval schedule. d-Amphetamine sulfate (courtesy of Smith, Kline and French Laboratories), chlordiazepoxide hydrochloride (courtesy of Hoffman-LaRoche, Inc.) and promazine hydrochloride (courtesy of Wyeth Laboratories) were dissolved in 0.9% sodium chloride solution and were injected in a volume of 1.0 ml/kg body weight into the calf muscle. d-Amphetamine and promazine were injected immediately before the session, chlordiazepoxide 60 min prior to the session. Doses are expressed in terms of the total salt. Drugs were generally given on Tuesday and Friday, given that Thursday's performance was stable when compared to performance prior to the beginning of each drug series. Doses were given in a mixed sequence on at least two separate occasions. d–Amphetamine was studied first followed by chlordiazepoxide and then promazine.

Analysis of Results

Drug effects are expressed as percent changes in control response rate. Average control rates of responding were obtained from five or more sessions conducted on Thursday or on a day when saline, rather than a drug, was injected. Control rates were separately determined during each phase of drug administration; changes in responding as a function of drug administration are expressed as a percentage change in control response rate prevailing during that particular drug sequence. Responses occurring during successive

fifths (1-min periods) of the FI were collected and cumulated over the session for each component of the schedule to permit an assessment of drug effects on local response rates occurring during different portions of the interval.

Quarter-life values, representing the average time taken for the first quarter of the responses to occur in the fixed-interval, expressed as a percentage of the duration of the interval, were computed under control conditions [10,12]. The quarter-life measure permits a comparison of patterns of responding under the present schedule with that obtained under other schedules of food presentation and stimulus-shock termination.

RESULTS

Control Performances

Comparable control rates and patterns of responding occurred under both components of the multiple schedule. Figure 1 shows cumulative response records of control performances under the food presentation and stimulus-shock termination schedules. Rates and patterns of responding were remarkably similar, despite differences in the consequent events that maintained responding. At the beginning of each component responding was characterized by a period of little or no responding followed by a gradually increasing rate that continued until food was presented or the stimulus-shock complex was terminated. Control response rates of both monkeys and quarter-life values for MS-28 increased over the 18-month period of the experiment; these increases occurred to an equivalent extent in both components of the multiple schedule (Table 1). Quarter-life values were low (about 31–34%) and patterning was less differentiated within the interval for MS-30 under both schedule components; these values and patterns were unchanged throughout the course of the study.

Effects of d-Amphetamine

Responding maintained under both the food-presentation and stimulus-shock termination schedules was increased substantially with d-amphetamine (Fig. 2). Cumulative response records (Fig. 1) and data taken from fifths of the interval (Fig. 3) show that the largest increases occurred in the lower rates of responding during the early portion of the interval. Figure 3 also indicates that average local rates of responding maintained by food-presentation and stimulus-shock termination were comparably affected; lower response rates were increased, whereas higher rates of responding were increased less or were unchanged from control values. There was no systematic relationship between changes in local response rates with amphetamine and the event that maintained responding. Identical results were also obtained with the second monkey in this study.

Effects of Chlordiazepoxide

The effects of chlordiazepoxide are shown in the dose-response curves of Fig. 2 and in the cumulative records presented in Fig. 1. Increases in responding maintained by food occurred with both monkeys at doses that did not affect or decreased responding under the stimulus-shock

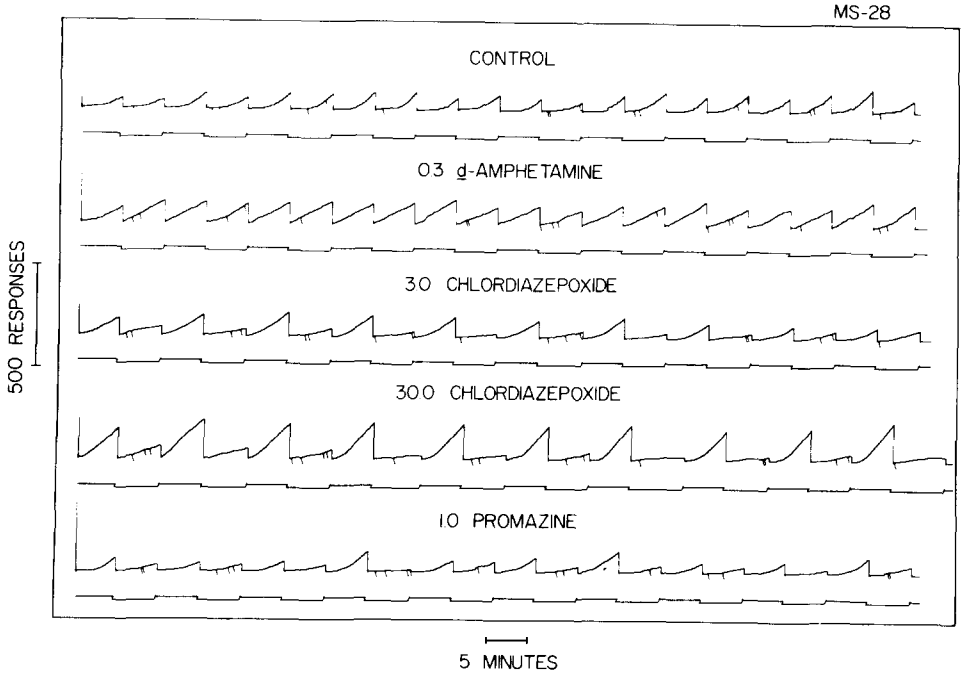

FIG. 1. Cumulative records of responding and drug effects under the multiple 5-min fixed-interval schedule of food presentation or stimulus-shock complex termination (MS-28). Ordinate: cumulative responses; Abscissa: time. Diagonal marks on the record denote the delivery of the response-independent shock; the event pen was displaced during the component in which responding terminated the stimulus-shock complex. The response pens reset at the termination of each fixed-interval and the cumulative recorder stopped during the one-min time-out period that followed each interval. Drug doses are in mg/kg.

TABLE 1

MEASURES OF PERFORMANCE UNDER THE MULTIPLE FIXED-INTERVAL SCHEDULES OF FOOD PRESENTATION AND STIMULUS-SHOCK TERMINATION DURING EACH SEQUENCE OF DRUG ADMINISTRATION

Animal	*d*-Amphetamine Food	*d*-Amphetamine Shock	Chlordiazepoxide Food	Chlordiazepoxide Shock	Promazine Food	Promazine Shock
Responses per second						
MS-28	0.064	0.068	0.194	0.178	0.252	0.250
	(± 0.009)	(± 0.008)	(± 0.016)	(± 0.011)	(± 0.011)	(± 0.010)
MS-30	0.166	0.171	0.241	0.261	0.354	0.358
	(± 0.011)	(± 0.013)	(± 0.032)	(± 0.024)	(± 0.009)	(± 0.023)
Quarter-life (%)						
MS-28	45	42	55	49	61	57
	(± 2.53)	(± 1.53)	(± 1.54)	(± 2.50)	(± 2.38)	(± 3.22)
MS-30	33	31	34	32	34	33
	(± 1.50)	(± 2.74)	(± 1.53)	(± 1.36)	(± 0.735)	(± 0.872)

Data represent the mean of between 5 and 8 nondrug or saline control sessions. Figures in parentheses represent ± 1 S.E.

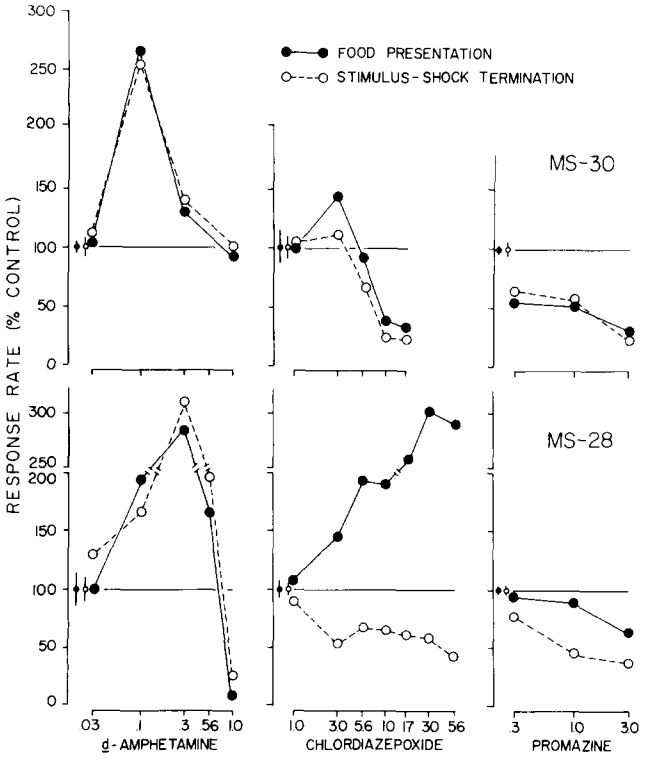

FIG. 2. Effects of *d*-amphetamine, chlordiazepoxide and promazine on responding under the multiple fixed-interval 5-min schedule of food presentation or stimulus-shock termination. Smaller symbols with vertical lines on the left of each dose-effect curve represent the mean ± 1 standard error of control response rates. Drug doses are given in mg/kg.

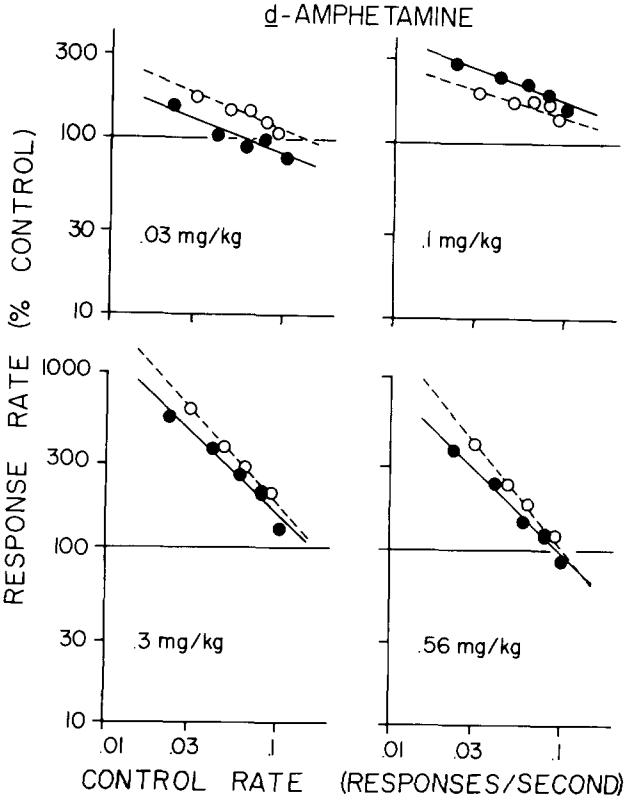

FIG. 3. Effects of *d*-amphetamine on mean local response rates during successive fifths of the fixed-interval (MS-28). Open circles and dashed lines represent responding under the stimulus-shock termination schedule, filled circles responding under the food-presentation schedule. Abscissa: control response rate (responses per second) obtained from successive fifths of the interval. Ordinate: response rate after drug as a percentage of the control rate. Both abscissa and ordinate are log scales. Note the comparability of response rates and drug effects on responding during successive fifths under both food-presentation and stimulus-shock termination schedules.

termination schedule. Larger increases in food-maintained responding occurred across a wider range of doses with MS-28 than with MS-30.

Figure 4 shows changes in local rates of responding with MS-28 with all doses of chlordiazepoxide. With the exception of the lowest dose (1.0 mg/kg), chlordiazepoxide produced unequivocally different effects on comparable local response rates under the food presentation and stimulus-shock termination schedules. Both regression lines were parallel across most doses; lower rates of food-maintained responding were increased substantially more than were comparable low rates of responding maintained by termination of the stimulus-shock complex. The lower rates of responding under the termination schedule were generally unaffected or were decreased with chlordiazepoxide. With MS-30, the second monkey in this study, low rates of food-maintained responding were also increased more or, at higher doses, were decreased less than were comparable rates of responding maintained under the stimulus-shock termination schedule (Fig. 5). As with MS-28, these differential effects of chlordiazepoxide on local rates of responding maintained by food and by stimulus-shock termination were most pronounced at doses above 1.0 mg/kg. Local rates of responding with MS-30 varied little throughout the interval (Fig. 5 and Table 1), a factor which may account for the slight differences in the effects of chlordiazepoxide on food-maintained performances between monkeys.

Effects of Promazine

Promazine decreased responding under both schedule components. With MS-28 these decreases were greater with responding that terminated the schedule-complex correlated with shock than in responding maintained by food (Figs. 1 and 2). These differences in overall rates following promazine administration with MS-28 are also reflected in the changes in local response rates at the 1.0 and 3.0 mg/kg doses (Fig. 6). As with chlordiazepoxide, promazine did not affect or decreased higher local response rates at doses that increased or decreased less the lower rates. With MS-28 lower local rates of food-maintained responding were increased and the higher rates decreased. Local response rates under the termination schedule were generally decreased with promazine, but lower rates were decreased to a lesser extent than were relatively higher rates. With MS-30 comparable local rates of responding under both schedules were similarly affected with promazine.

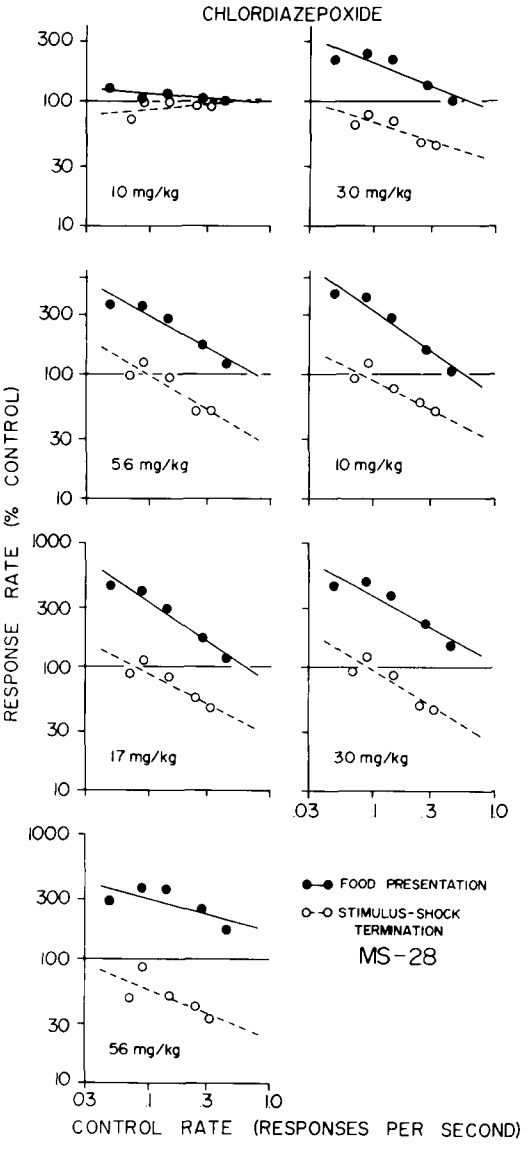

FIG. 4. Effects of chlordiazepoxide on local control response rates (MS-28) during successive fifths of the fixed-interval schedules of food presentation (closed symbols) and stimulus-shock termination (open symbols). Chlordiazepoxide produced effects that depended on the maintaining event. Data expressed as in Fig. 3.

DISCUSSION

Behavioral performances maintained in the present study did not depend on whether food presentation or termination of a stimulus associated with shock were scheduled as different consequent events. These findings are in agreement with other experiments demonstrating that dissimilar events can engender and maintain comparable performances when the schedules under which those events occur are similar (e.g., [19,20]).

In most previous experiments that have maintained responding under fixed-interval schedules of termination of a stimulus associated with shock, shocks were scheduled to occur at the end of the interval, after an elapsed time (t sec), and to recur until a response terminated the schedule complex [13, 16, 18]. In the present study shocks occurred under a variable-time schedule, independently of responding, throughout the fixed-interval cycle. Positively accelerated responding, typical of that obtained previously (e.g., [18]), occurred with MS-28 under the present schedule conditions; quarter-life values and patterns of responding with this monkey were comparable to those reported by Morse and Kelleher [18] at certain values of t. Response rates of the monkeys in the present study were also comparable to those found by Morse and Kelleher [18]. The dependence of the rate of responding on the t value (or shock frequency in the present experiment) and shock intensity make straightforward comparisons difficult. It appears, however, that variable intermittent and response-independent shocks delivered throughout the interval can engender typical fixed-interval patterns of responding.

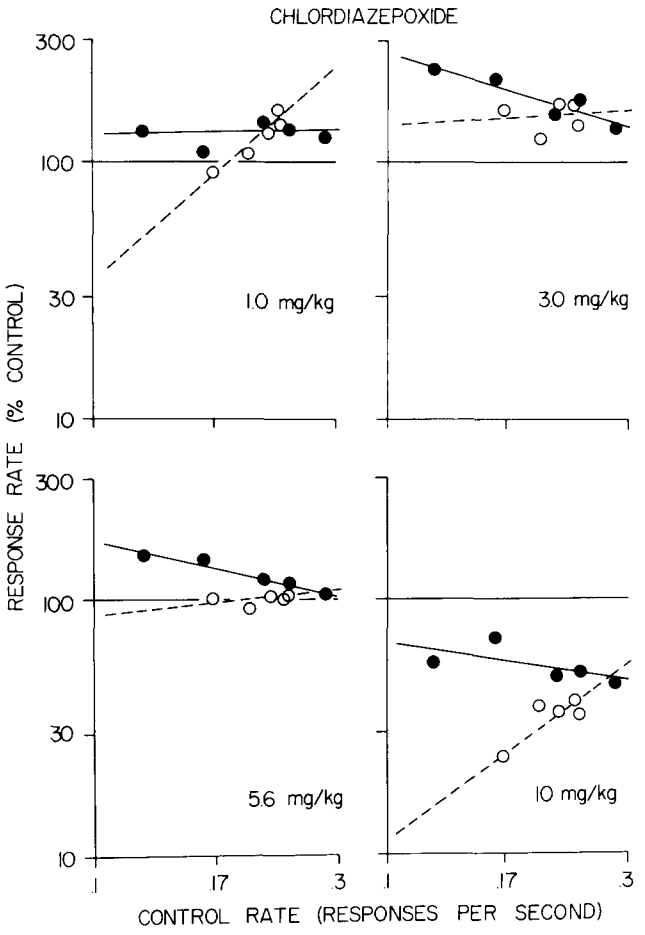

FIG. 5. Effects of chlordiazepoxide on local control response rates (MS-30) during successive fifths of the fixed-interval schedules of food presentation (closed symbols) and stimulus-shock termination (open symbols). Data expressed as in Fig. 3.

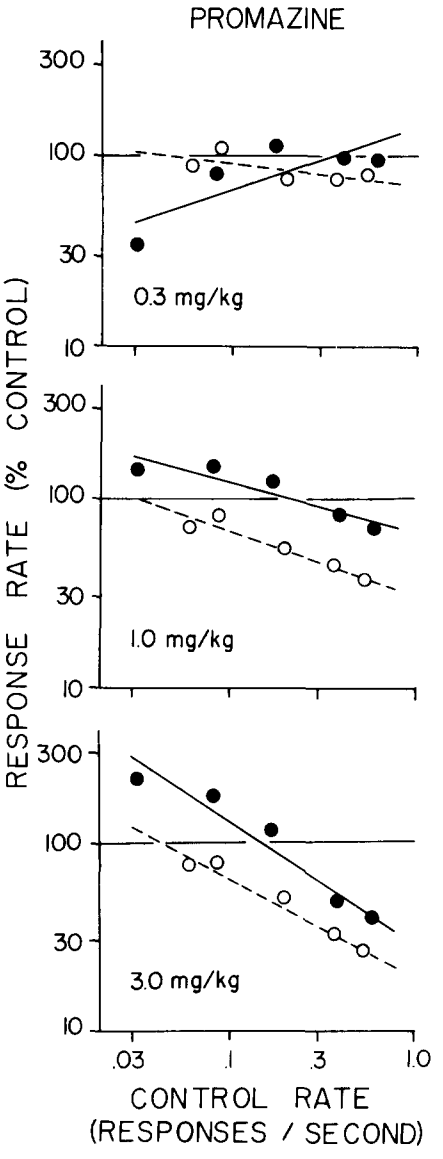

FIG. 6. Effects of promazine on response rates (MS-28) during successive fifths of the 5-min fixed-interval schedules of food presentation (closed circles) and stimulus-shock termination (open circles). Data expressed as in Fig. 3.

It is not possible to account for factors that could have contributed to the relatively lower degree of patterning (as reflected in the low quarter-life values, Table 1) with MS-30 under both schedules of the present experiment. Morse and Kelleher [18] also reported difficulty in obtaining characteristic fixed-interval patterns under conditions where responding terminated a schedule complex under which intermittent shocks were delivered throughout the interval. It may be important, however, that patterning typical of that under the fixed-interval schedules also never developed under the food-presentation schedule with MS-30. An adequate evaluation of performances engendered under the two different schedules of stimulus-shock termination must await further systematic comparisons across a range of parameter values.

A schedule of termination of a stimulus where shocks occur at variable times throughout the fixed-interval cycle could be useful in experiments where the effects of variables that potentially decrease responding are being investigated. When shocks are scheduled to occur at the end of the fixed-interval, decreases in response rate could result in substantial increases in shock frequency, a change which could interact with the variable of interest. Marked changes in the frequency of shock presentation are not likely to accompany even substantial decreases in responding when shocks are delivered under a variable-time schedule throughout the fixed-interval cycle. This feature could be advantageous when assessing the effects of drugs or other interventions on responding when it would be desirable to minimize changes in the schedule which occur as a consequence of changes in performance.

The effects of d-amphetamine and promazine on responding in the present study did not depend on the maintaining events. Amphetamine increased responding maintained by food presentation or by termination of a stimulus-shock complex; promazine only decreased responding under these conditions. These results are comparable to those generally reported for drugs which belong to these classes (e.g., [13, 15, 23, 24]). Under a wide range of conditions and with different consequent events, the

effects of the amphetamines and phenothiazines seem to depend critically on the schedule-controlled rate and pattern of responding and not on the maintaining event.

Chlordiazepoxide, however, produced different effects on responding in the present study depending on whether food or stimulus-shock termination maintained responding. Increases in responding maintained under fixed-interval schedules of food delivery with chlordiazepoxide have been reported often [1, 2, 3, 4, 22] and appear to have wide generality across species and interval schedules [6]. Responding maintained by termination of the stimulus-shock schedule was only decreased with chlordiazepoxide in the present study. Cook and Catania [3] also found decreases in responding maintained under a fixed-interval schedule of termination of a 2.5 mA continuous shock. This effect, however, depended on shock intensity and on the baseline response rate. When the shock intensity was 0.8 mA and response rate was approximately 2 responses per min (compared to approximately 9 responses per min at the 2.5 mA intensity), chlordiazepoxide produced substantial increases in responding. Since the present experiment focused on an effort to compare the effects of drugs on equivalent rates of responding maintained by dissimilar events, no assessment was made of the contribution of shock intensity and response rate to the effects of chlordiazepoxide.

That differential drug effects can be obtained when similar rates of responding are controlled by different events is in agreement with recent findings indicating that the maintaining event can determine the effects of certain drugs on behavior [1, 15, 16]. The dependence of drug effects on the type of maintaining event is undeniably important for a thorough understanding of factors contributing to the behavioral effects of drugs. Controlling events can be significant determinants of drug effects, but their contribution must be assessed in conjunction with other variables such as the schedule-controlled rate and pattern of responding, the context in which behavior occurs, and the behavioral history of the organism (cf. [17,21]). Under certain circumstances, any one of these variables may be of overriding significance in determining the effects of a drug on behavior.

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