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Drug Effects Upon Force and Duration of Response During Fixed-Ratio Performance in Rats[1]

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FOWLER, S. C., R. J. FILEWICH AND M. R. LEBERER. *Drug effects upon force and duration of response during fixed-ratio performance in rats.* PHARMAC. BIOCHEM. BEHAV. 6(4) 421–426, 1977. - Rats responded on a tandem FR24CRF CRF CRF CRF schedule of water reinforcement by paw-pressing a silent, isometric, force-sensing manipulandum. Oral dose ranges of d-amphetamine, chlordiazepoxide, chlorpromazine, and dantrolene were evaluated for their effects on this schedule-controlled behavior. Peak force, duration and interresponse time (IRT) of individual responses were recorded with a laboratory computer system. Conjoint examination of these three dependent variables revealed that the intensitive measures of response (i.e., peak force and duration) provided information about drug effects that could not be detected with the conventional IRT measure alone. More specifically, peak force was elevated by d-amphetamine at 1.6 mg/kg during the FR component, but IRT was unaffected at this dose. At 3.2 mg/kg, d-amphetamine decreased peak force and lengthened IRT during the FR component. Chlordiazepoxide increased peak force up to the highest dose examined (27.0 mg/kg), whereas dantrolene decreased peak force. Chlorpromazine did not affect peak force but did increase response duration. Higher doses of chlordiazepoxide, chlorpromazine, and dantrolene lengthened IRT during the FR component. For all three dependent variables drug effects were generally less pronounced or altogether undetected in the CRF component. The results are discussed in relation to explanatory principles such as rate-dependency and stereotyped behaviors.

Response force Duration Interresponse time D-amphetamine Chlordiazepoxide
Chlorpromazine Dantrolene Rat

WEISS and Gott [20] conducted an interresponse time (IRT) analysis of the effects of drugs upon fixed-ratio (FR) responding. Their microanalysis suggested that behaviorally active drugs such as amphetamine and pentobarbital may act primarily on FR cohesiveness and that drug effects on IRT during FR responding appear to depend upon specific portions of the FR cycle. In discussing their data, Weiss and Gott [20] offer the general observation that a clear explanation of behavioral drug effects may have to be "formulated in terms of rather fundamental events at the level of the individual response and its properties (p. 202)." Accordingly, the purpose of the present research was to examine the effects of several classes of drugs upon FR behavior in terms of the intensitive properties of individual responses. Thus, in addition to IRT, peak force of response and duration of response were measured during FR responding, and effects of dose ranges of d-amphetamine, chlordiazepoxide, chlorpromazine, and dantrolene were assessed with these techniques. The first three of these four drugs were selected because they were among the conventional ones used for evaluation of new behavioral methods. Dantrolene, which exerts its relaxant effect by acting directly upon skeletal muscle (see, e.g., [5]), was included for study to provide a behavioral comparison with chlordiazepoxide, which possesses muscle relaxing properties of predominately neurological origin.

On a purely empirical level, it can be argued that force of response is a reflection of the motor features and/or topographical variants of behavior. Thus, force of response as a dependent variable may supply important information about drug effects which is not observable with rate measures alone (see [6,7,17]). Moreover, previous research suggests that response force and response rate may not necessarily covary. For example, Fowler [7] showed that response force remains elevated during the first 8 min of extinction while rate declines. Because rate and force of response may measure different aspects of behavior, an analysis of operant responding that includes the intensitive

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response variables should contribute to a more complete understanding of the manner in which schedule-controlled behaviors are modified by drugs. For instance, Sanger and Blackman [8] have suggested that the rate-dependency hypothesis, which posits that the effect of a drug on response rate depends upon the baseline rate of responding [2,4,12], may be further evaluated by designing experiments "which assess in more detail the importance of variables other than simple response rate (p. 80)." Conjoint examination of response force, response duration and IRT in the present research was seen as an attempt to conduct experiments of the kind suggested by Sanger and Blackman.

METHOD

Animals

The animals were 11 male Sprague-Dawley rats (Holtzman Co.) with body weights averaging about 225 g. These animals were maintained under conditions of water deprivation which permitted 20 min access to water approximately 30 min after each daily session of responding. Except for the 3 hr period prior to a session, food was continuously available in the individual home cages.

Apparatus

Constructed from Plexiglas, sheet aluminum, and stainless steel rod, the conditioning chamber measured 23 cm long, 20 cm wide and 19 cm high. An opening in the front panel of the chamber was 3.0 cm wide and 2.5 cm high and permitted access to the manipulandum, which was positioned outside the chamber. The lower edge of the manipulandum aperture was 5.5 cm above the grid floor. A Sanborn force transducer (Model FTA-100) served as the isometric manipulandum (downward excursion of 0.4 mm at a force of 200 g). This transducer is an LVDT (linear variable difference transformer) and is capable of measuring both static and dynamic forces. (In an unloaded condition, its natural frequency is 390 Hz.) The portion of the transducer available to the animal was a horizontal disk 18 mm in diameter, the surface of which was 60 mm above the grid floor. The manipulandum was positioned so that the center of the disk was 30 mm from the outside of the chamber wall. Protruding into the chamber from the lower right front of this wall was a stainless steel drinking cup, which was serviced by a solenoid valve that permitted delivery of calibrated volumes of water. The chamber, manipulandum, and solenoid valve were enclosed in a sound-attenuating compartment.

Programming of contingencies and recording of data were accomplished by means of a minicomputer (PDP8/e) interfaced with an analog-to-digital (A/D) converter, an incremental magnetic tape recorder, and conventional relay equipment. The apparatus was programmed to record peak force of response, duration of response, and IRT. Details of these techniques may be found in [8]. Briefly, the A/D converter sampled the analog voltage from the transducer every 0.01 sec. From these measurements the properties or individual responses above a 4 g threshold (c.f., [16]) were computed on-line. The peak force of a response is simply the maximum force amplitude attained by a response. Duration of response is the amount of time that force remains above threshold. IRT is the time elapsing from the falling of the preceding response below threshold to the rising of the succeeding response above threshold. Thus response duration is entirely separated from IRT. Response duration and IRT were measured with a precision of ± 0.01 sec, and peak force was recorded with a precision of ± 0.5 g.

Procedure

The animals were manually shaped to reach through the aperture in the chamber wall to exert downward vertical force on the manipulandum. This procedure was undertaken to develop relatively uniform response topography and to preclude biting. Throughout the experiments, the reinforcer was delivered upon response termination. This is an important procedural detail because the presentation of the reinforcer and accompanying solenoid click could not serve as an exteroceptive cue for attainment of the reinforcement criterion. In other words, the silent, isometric manipulandum provided no exteroceptive cues. If the reinforcer had been delivered at the instant that the force criterion of 4 g was attained, it seems likely that the reinforcer would have become an S^D for the rat to terminate the response, thereby possibly relegating the peak force variable to control by solenoid operation and limiting the extent to which this dependent variable would be free to vary. Moreover, delivery of the reinforcer upon response termination is consistent with the procedures used in the majority of reported operant conditioning experiments on the dynamic properties of individual responses (see e.g., [8, 9, 16]).

Preliminary to assessment of drug effects, all subjects received 50 daily sessions of FR24, 20 cycles per session; then 40 sessions of tandem FR24 CRF CRF CRF CRF (that is, 24 unreinforced responses, unaccompanied by any exteroceptive stimulus, followed by 4 reinforced responses, etc., hereafter referred to as tand FR24CRF) ensued. The schedule may also be properly designated as a mixed FR25FR1, however, the tandem nomenclature is adopted here to emphasize the fact that four successive responses were reinforced in the CRF component. This somewhat unconventional schedule was chosen because Mintz [15] demonstrated that such a procedure engenders relatively high forces during the FR component and lower forces during CRF. Therefore, it was anticipated that the tand FR24CRF schedule would provide two different baseline values for mean peak force of response. For the last 10 preinjection sessions and for all of the subsequent drug and saline sessions, the reinforcer volume was 0.20 ml. The peak force criterion for reinforcement and for advancing the ratio count was 4 g throughout. A session continued for 20 cycles of the tandem schedule or for 30 min, whichever occurred first. Sessions were programmed to begin and end with the CRF component.

Drugs were administered by gavage 45 min before the subject was placed in the experimental chamber and were given every third day. In all cases drugs were diluted with sufficient saline to yield a dose volume of 1.0 ml. The day before each drug session, 1.0 ml of saline was intubated. On nonintubation days, following each drug day and preceding each saline day, animals were merely exposed to the conditioning procedures. Before the first drug day, animals received 4 successive saline sessions to accustom them to the intubation procedure. The drugs and dosages (expressed as the salt) were given in randomized order. Six animals received d-amphetamine (Smith, Kline, and French; 0.4, 0.8, 1.6, and 3.2 mg/kg), chlorpromazine (Smith, Kline, and French; 0.3, 1.0, 3.0, 9.0 mg/kg), and chlordiazepoxide

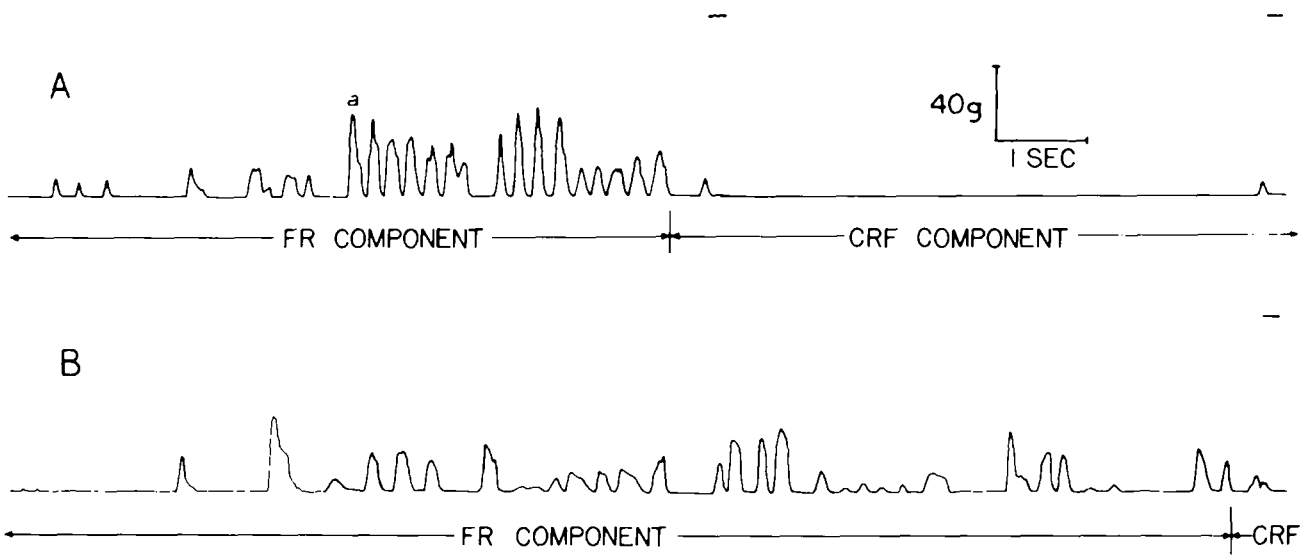

FIG. 1. Strip-chart recordings of instantaneous response force as a function of time during a saline control session (tracing A) and after 3.2 mg/kg of d-amphetamine (tracing B). The horizontal event markers at the upper margin of each recording represent the delivery of 0.20 ml of the water reinforcer. The response labeled a in the upper recording had a peak force of about 46 g.

(Hoffman-LaRoche: 1.0, 3.0, 9.0, 27.0 mg/kg). The other 5 subjects only received doses of sodium dantrolene (Eaton; 12.5, 25.0, 50.0, 100.0 mg/kg). One determination of drug effect was made at each dose. The data from six of the saline sessions were selected randomly from the available saline sessions, and these data were averaged to produce the baselines against which drug effects were assessed.

RESULTS

The top strip chart recording in Fig. 1 shows a representative portion of a saline session. The horizontal event marks in the CRF component signify delivery of the reinforcer. It can be seen that relatively high peak force of response is associated with the FR component of the schedule, while comparatively low force is emitted during the CRF component. This result is similar to that originally reported by Mintz [15], and by Notterman and Mintz [16]. Responses which immediately follow the reinforcer have low peak force, short durations, and long IRT's compared to the responses which are emitted during the FR component. Even after more than 90 sessions on the tandem schedule, all subjects displayed these patterns of responding. Figure 1 indicates that very high rates of responding can be achieved by rats under these circumstances. Many of the IRT's are as brief as 0.10 or 0.20 sec.

In view of the large differences between response measures engendered by the two components of the tand FR24CRF schedule, the assessment of drug effects was based on each component considered separately. These data for the four drugs are presented in Fig. 2. Performance on the CRF component was considered to be represented best by the four responses that followed reinforcer delivery; the lowest average peak forces and the longest average IRT's were associated with these responses. Likewise, the high-rate, high-force portion of the FR component was summarized by considering together the 20 responses preceding the CRF component. These 20 responses, on the average, were emitted at a relatively constant, high rate (see Fig. 1, record A), and they are most representative of the vigorous output characteristic of FR performance.

Amphetamine. D-amphetamine significantly affected peak force of response, $F(4,45) = 13.766$, $p < 0.01$ and IRT, $F(4,45) = 4.502$, $p < 0.01$, but it did not reliably influence response duration, $F(4,45) = 2.500$, $0.05 < p > 0.10$. Figure 2 indicates that the relation between dose of amphetamine and peak force during the FR component is nonmonotonic. The 1.6 mg/kg dose increased peak force substantially, whereas the 3.2 mg/kg dose resulted in a large decrease in peak force compared to saline control values. The effect of 3.2 mg/kg is illustrated for one subject by tracing B in Fig. 1. In this recording it is apparent that peak force is reduced, IRT is lengthened, and the consistency of the force emissions is impaired during the FR component. That the drug effects are more pronounced for the FR component is manifested by randomized block factorial analyses of variance for peak force and IRT. For both of these dependent variables there is a significant interaction between schedule component and drug dose: $F(4,45) = 3.814$, $p < 0.05$ for peak force, and $F(4,45) = 3.126$, $p < 0.05$ for IRT. Thus the drug effect depends upon the baseline values of peak force and IRT.

Chlordiazepoxide. This minor tranquilizer significantly increased peak force and duration of response, while lengthening IRT at the higher doses (see Fig. 2). Despite the graphic differences in slopes of the peak force-dose curves for the two schedule components, the lack of a significant interaction, $(4,45) = 0.256$, $p > 0.10$, in the analysis of variance suggests an absence of a force-dependency effect under these circumstances. However, the interaction term for the IRT measure is statistically significant: $F(4,45) = 4.127$, $p < 0.01$. Response duration was increased by chlordiazepoxide (main effect of dose gave an $F(1,45) = 3.085$, $p < 0.05$), the increase being apparent for both the CRF and FR components (interaction not significant, $F(4,45) = 0.496$, $p > 0.10$).

Chlorpromazine. Both the graphic data in Fig. 2 and the analysis of variance show that chlorpromazine did not affect mean peak force $F(4,45) = 1.811$, $p > 0.10$. On the

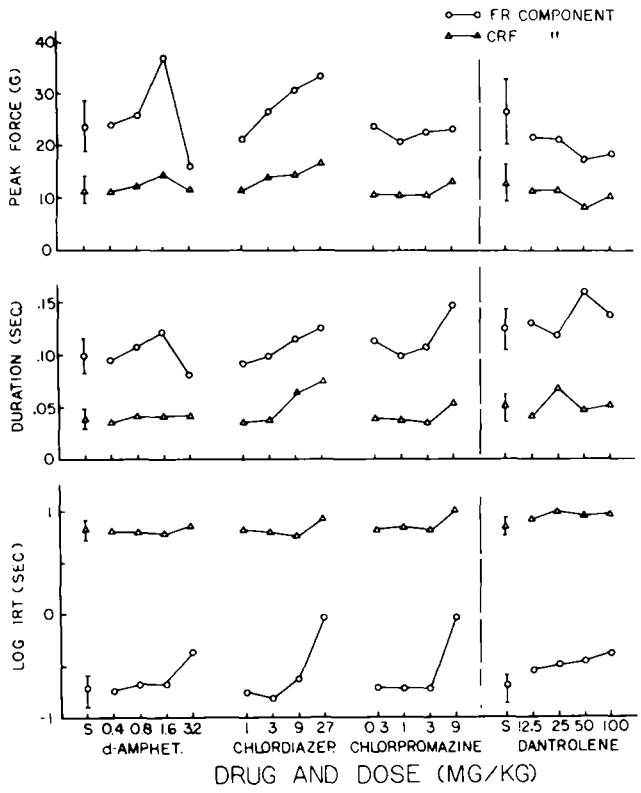

FIG. 2. Dose-response functions for peak force, duration and $\log_{10}$ IRT. S on the abscissa signifies a mean of six saline control sessions, and the vertical bars for the saline sessions indicate the 0.95 confidence interval for these values. The same six rats received d-amphetamine, chlordiazepoxide (chlordiazep.), and chlorpromazine. Dantrolene was administered to a separate group of five rats.

other hand, the highest dose increased duration, $F(4,45) = 6.114$, $p<0.01$ and increased IRT, $F(4,45) = 15.685$, $p<0.01$. However, a significant interaction between drug dose and schedule component emerged only for the IRT variable, $F(4,45) = 4.056$, $p<0.01$.

Dantrolene. Dantrolene was administered to a separate group of five subjects as a precaution because the relatively high doses coupled with a comparatively long half-life [10] could have produced carryover effects. As shown in Fig. 2, dantrolene had its most systematic effect on peak force of response. For both FR and CRF components response force was depressed relative to saline performance across the range of doses. The magnitude of the effect even at the lowest dose used suggests that the dose range was probably rather high. Nevertheless, the result for response force appears genuine, $F(4,36) = 3.525$, $p<0.05$. The analysis of variance for response duration revealed a significant effect of dose; $F(4,36) = 7.415$, $p<0.01$. Despite the graphic trend in Fig. 2, the effect of dantrolene on IRT did not quite achieve statistical significance, $F(4,36) = 2.130$, $0.05<p>0.10$.

DISCUSSION

The pattern of drug effects on IRT during the FR component was highly similar for d-amphetamine, chlordiazepoxide, and chlorpromazine. The general trend is for IRT during FR to be lengthened by these three drugs at the higher doses. This finding is consistent with reports in the literature involving FR schedules of comparable ratio length [1,3,20]. Over the same range of doses for d-amphetamine, chlordiazepoxide, and chlorpromazine, the peak force variable displays a dose-related pattern that is distinctly different from that seen for the IRT variable. Low doses of d-amphetamine increased peak force, whereas the 3.2 mg/kg dose reduced peak force compared to saline control conditions. The dose level of chlordiazepoxide had a monotonic force-increasing influence up to the highest dose used. Chlorpromazine did not affect peak force. From a strictly empirical point of view, the lack of correspondence between the IRT and peak force variables for the same doses in the same subjects suggests that the methods used here may contribute to the continuing development of procedures for separating psychoactive drugs according to distinctive behavioral effects.

Another important issue to which the current data are germane is the widely-held hypothesis that behavioral drug effects frequently depend upon the schedule of reinforcement and other conditions maintaining the operant behavior. The analyses of variance for the dose-related effects of d-amphetamine, chlordiazepoxide, and chlorpromazine on IRT clearly suggest, by virtue of the significant interactions, a rate-dependency effect [4,12,18]. It will be recalled that the FR component of the tand FR24 CRF schedule produced relatively short IRT's and high peak forces, while the converse was true for the CRF component. The rate-dependency lies in the fact that high rates were decreased by the drugs, but low rates were relatively unaffected by the drugs. Interestingly, only the drug d-amphetamine produced a significant force-dependency effect, and this is the drug for which the rate-dependency effect appears to be most pronounced [18].

The foregoing considerations do not explain the particular shapes of the functions relating peak force to drug dose for the FR component. Additional principles appear to be required. In the case of d-amphetamine, Lyon and Randrup [13] have suggested that the behavioral effects of this drug are closely associated with the emergence of stereotyped behaviors. More specifically, they propose that d-amphetamine stimulates behavioral output, but does so in such a way that the classes or kinds of behavior emitted decrease with increasing dose. Under higher doses (greater than about 3 mg/kg, IP) stereotyped behaviors intensify to the exclusion of bar-pressing behavior. At lower doses d-amphetamine produces an increase in the output of whatever behavior is occurring (e.g., bar pressing). In the present study d-amphetamine at 1.6 mg/kg (by gavage) increased peak force during the FR component. However, IRT during FR was not appreciably affected by this dose, probably because the baseline rate was already maximal (but baseline peak force was not maximal even though it was stable). On the other hand, the 3.2 mg/kg dose not only reduced rate but also produced a different kind of responding, as evidenced by the peak force measured and by the pattern of responding (see Fig. 1, recording B). The lowered forces and lengthened IRT's at 3.2 mg/kg may be viewed as manifestations of an increasing tendency for nonmanipulandum-oriented behaviors to occur. Thus the data reported here for the peak force variable are not inconsistent with Lyon and Randrup's [13] theory. Moreover, the amphetamine-induced disruption of FR cohesiveness reported by Weiss and Gott [20] may be understood in the same terms.

The drug chlordiazepoxide increased peak force of response in a dose-related fashion. Further, the heightened force emission was clearly evident at the 27.0 mg/kg dose, which had a marked slowing effect on rate during the FR run. Thompson [19] has reported that chlordiazepoxide increases the breaking point in a progressive ratio schedule, and Fowler [7] found that chlordiazepoxide led to response forces in extinction that were significantly higher than saline control values also recorded during extinction. The response force variable may reflect the fact that chlordiazepoxide increases behavioral output in aversive situations, even if the aversiveness is created by high levels of exertion instead of by punishment procedures. Previous studies have shown that FR schedules and extinction engender in rats relatively high effort expenditure per response despite the lack of any experimental requirement for such effortful behavior [7,16]. From a methodological point of view, the importance of the present measurement technique lies in its ability to dissociate simultaneously in a single drug an apparent energizing effect from a sedative or slowing effect.

Comparison of the response-force results for chlordiazepoxide and dantrolene permits a further refinement of the statements that can be made about the action of chlordiazepoxide. For dantrolene, response force was clearly reduced, but for chlordiazepoxide, it was obviously increased. Since dantrolene acts directly on the skeletal muscle tissue [5] to produce its relaxing effect, it seems likely that the force-increasing effect of chlordiazepoxide was not the result of chlordiazepoxide's own muscle-relaxing properties alone. Muscle relaxation per se is probably not a key to understanding the effects of chlordiazepoxide on response force.

The response duration data deserve special comment because of the previously observed positive correlation between peak force and duration of response [16]. Using procedures for CRF similar to those implemented here, Notterman and Mintz [16] found a positive correlation between peak force and duration of about + 0.70 (see page 68 in [16]). The correlation arises from the fact that higher peak forced simply require more time for their emission. The phenomenon is illustrated in Fig. 1: the three low-force responses at the extreme left of recording A have much shorter durations than the response a, even though the latter is quite ballistic. In view of such a relationship, the duration data may simply be a reflection of peak force changes, or, alternatively, duration may provide additional information in its own right. In cases where peak force is reduced or unchanged by a drug, the emergence of a drug effect on duration cannot be attributed to the positive correlation between duration and peak force. For example, chlorpromazine did not significantly affect peak force, but this neuroleptic did lengthen response duration at the highest dose (see Fig. 2). Thus, the duration effect is genuine and appears consistent with the thesis that chlorpromazine simply slows most behavioral processes [11]. Likewise, dantrolene increased duration while reducing peak force. Therefore, these duration measures for chlorpromazine and dantrolene suggest a sluggishness of individual responses emitted by rats. In contrast, the dose-related effects of chlordiazepoxide on duration covary directly with peak force, thereby implying that the duration increase was, at least in part, a consequence of the higher forces produced by chlordiazepoxide.

Despite procedural differences between the experiment performed by Weiss and Gott [20] and the research reported here, the two investigations are in agreement in their general implications. Judgments about the sensitivities to drug effects of various schedule-controlled behaviors could benefit from an analysis of the properties of individual responses. Just as one cannot accurately predict a drug's effect upon response rate without specifying the conditions which maintain the behavior [14], one cannot assume that all dependent measures of operant behavior will provide parallel characterizations of a drug's effects.

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