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Rate Dependent Drug Effects: Possible State Dependency[1]

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KSIR, C. *Rate dependent drug effects: possible state dependency.* PHARMAC. BIOCHEM. BEHAV. 4(2)165–168, 1976. – Of 6 rats given extensive experience responding on a fixed-interval reinforcement schedule after injections of 1 mg/kg d-amphetamine, 3 showed significant rate dependent changes in responding when presession saline was substituted for d-amphetamine. Low rates were increased and high rates decreased by the change from d-amphetamine to saline, a result commonly found when d-amphetamine is first introduced. This indicates that rate dependent changes in fixed-interval responding may be state dependent phenomena.

Rate dependent drug effects d-Amphetamine State dependency Reinforcement schedule

ONE popular method in behavioral pharmacology has been the use of fixed-interval schedules of reinforcement to produce a variety of baseline response rates against which the effects of drugs on behavior may be studied [1]. In such a schedule, an animal (typically food deprived) is enclosed in a chamber which contains some type of response key. The first response on that key after a given amount of time has elapsed is followed immediately by a reinforcing event (typically access to food). The specification of a time interval defines the schedule (e.g. fixed-interval 5 min; FI 5 min). Under a variety of interval lengths and in a variety of species, such a schedule produces low rates of responding early in the interval, with the response rate increasing to some high terminal rate near the end of the interval [5]. The effects of amphetamine on such responding may be described as rate dependent; that is, the amount and even the direction of drug-induced change in response rate depends directly on the predrug rate of response. The rate dependency holds when performances on different schedules which generate different response rates are compared, and whether the reinforcing event is food delivery or termination of electric shock [5]. Specifically, amphetamine tends to increase the low rates early in the interval, increase less those rates intermediate in the interval, and sometimes decrease the high rates near the end of the interval. Rate dependent effects of a similar nature have been found for amobarbital [8], diazepam, chlordiazepoxide, pentobarbital and chlorpromazine [11], nicotine [12], mescaline [14] and scopolamine [9]. Although the tendency to increase or decrease overall FI rates may vary among these drugs, the finding of a rate dependency is common to all of them, at least at some doses. Although the evidence is limited, it appears that some drugs may not produce rate dependent effects at behaviorally active doses. Such limited evidence exists for LSD [14] and two forms of THC [3], as well as a few other drugs [10].

The phenomenon of rate dependency is of practical importance to behavioral pharmacologists because it means that most drugs cannot be classified as enhancers or diminishers of responding. An increase, decrease, or no change in response rate is important only when considered in relation to the predrug response rate and to the effects of the same dose of the same drug on other response rates. In spite of the practical importance of the phenomenon, there has been little discussion of the theoretical basis of rate dependent drug effects.

McKim [9] pointed out that similar effects on FI performance may be obtained by changing the key color for a pigeon, or by presenting other novel stimuli such as noise or vibration to a rat [2,4]. These studies showed that a stimulus change could increase responding in the first half of the interval, and decrease responding in the second half of the interval. A more complete rate dependent analysis has been made possible by a recent publication [15]. Key pecking was maintained in pigeons on an FI schedule with a vertical line projected on the response key. The line was then tilted left or right, either 22.5° or 45°, on different sessions. Each pigeon experienced all line tilts, and no change was made in reinforcement contingencies. Since data were given for each 1/3 of the interval, it was possible to calculate rate-dependent functions. These are shown in Fig. 1. It is clear that the line tilts increased the previously low response rates early in the interval, decreased the previously high rates late in the interval, and had little effect on the intermediate rates in the middle of the

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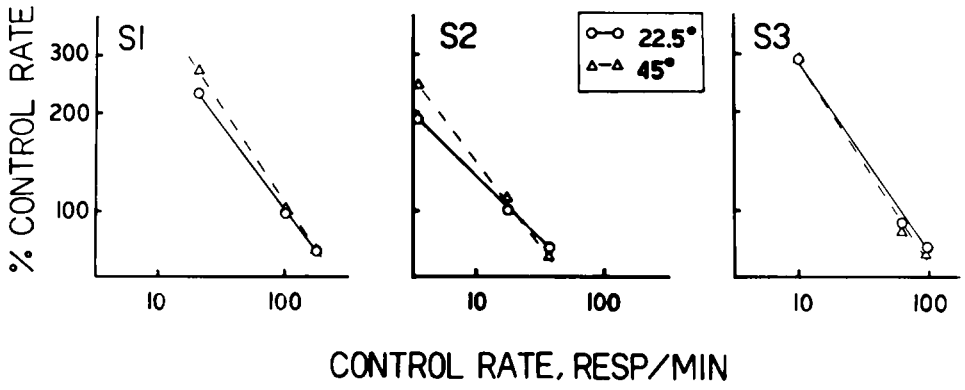

FIG. 1. The effect on response rates in each third of an FI schedule of tilting a line projected on the response key. Rates when the lines were tilted have been calculated as percentages of the corresponding rates when the standard vertical line was projected. Redrawn from Wilkie [15].

interval. The points fell close to a straight line on this plot (both axes on logarithmic scales). This is exactly the sort of rate dependent effect produced by many drugs.

If rate dependent drug effects are the result of stimulus change, then animals which receive FI training following amphetamine injections should exhibit rate-dependent changes in behavior when saline injections are substituted for amphetamine.

METHOD

Animals

Six male Long-Evans-derived hooded rats, 90–120 days old at the beginning of the experiment, were used. Each rat was housed individually, with free access to food in the home cages. Rats were given access to water for approximately 20 min following each daily session, Monday – Thursday, and were allowed access to water for approximately 24 hours following the Friday session. Water was again given for 20 min on Sunday.

Apparatus

All sessions were conducted in a standard operant conditioning chamber which contained a Gerbrands Model B response disc mounted on one end wall approximately 3 cm above the grid floor. A brass spigot projected from the center of the same end wall at the same height. This spigot allowed the dispensing of a 0.1 ml drop of 9% sucrose solution as a reinforcer. Events in the chamber were controlled and recorded by a Texas Instruments 960A computer [7].

Procedure

Rats were trained to press the response disc by presenting a reinforcer after each response. The minimum time between reinforcements was increased over several daily sessions until a FI 3-min schedule was in effect: the first response after 3 min had elapsed produced a reinforcer. Each session consisted of 10 complete intervals.

Drugs were injected intraperitoneally 30 min before the session in a volume of 1 ml/kg. D-amphetamine sulfate, 1 mg/kg, was given to Rats 7416, 7417, and 7418 before each daily session, beginning with initial response training. Those rats were given d-amphetamine before each of 22 sessions on the FI 3-min schedule. Before the next and subsequent sessions, 0.9% NaCl (saline) was injected. Rats 7419, 7420, and 7421 were given saline injections during training and for the first 22 sessions on FI3. They were then given 1.0 mg/kg d-amphetamine for 24 sessions before changing back to saline injections. For all changes, new injection solutions were given for the first time on a Thursday session.

RESULTS

For each rat, the average response rate in each 1/10th of the interval was determined for the 2 sessions before a change in injection and for the 2 sessions following a change. The postchange values were then calculated as percentages of the corresponding prechange response rates. Figure 2 shows the effect of changing from saline to d-amphetamine for Rats 7419, 7420, and 7421. Regression lines through each set of points give an indication of the rate dependent effects of d-amphetamine: the slopes for 7419 (−0.73) and for 7420 (−0.47) were significantly different from zero (Fs = 957 and 87, df = 1,8, $p<0.001$). The slope for 7421 (0.24) was not significant (F = 2.0, df = 1,8).

Figure 3 gives the results for all the rats of changing from d-amphetamine to saline. No signfiicant change in performance was seen in Rats 7416 or 7417 (slopes = −0.10, −0.02; Fs = 2.3, 0.1; df = 1,8). Rat 7419 showed a tendency toward further reduction in low rates with little change in higher rates, however this effect was not significant (slope = 1.23, F = 4.0, df = 1,8). For Rats 7418, 7420, and 7421, changing from d-amphetamine to saline produced significant rate dependent effects: for 7418, slope = −0.43 (F = 11.36, df = 1,8, $p<0.01$), for 7420, slope = −0.67 (F = 138.3, df = 1,8, $p<0.001$), and for 7421, slope = −0.47 (F = 8.8, df = 1,8, $p<0.025$).

DISCUSSION

The present experiment demonstrates that it is possible to produce rate dependent changes in behavior of the type seen when various drugs are administered by changing from a consistent drug state to a nondrug state. Although the effect was seen in only three of the 6 rats tested, it should be pointed out that rate dependent effects are not always seen after acute drug administration. Only two of three rats

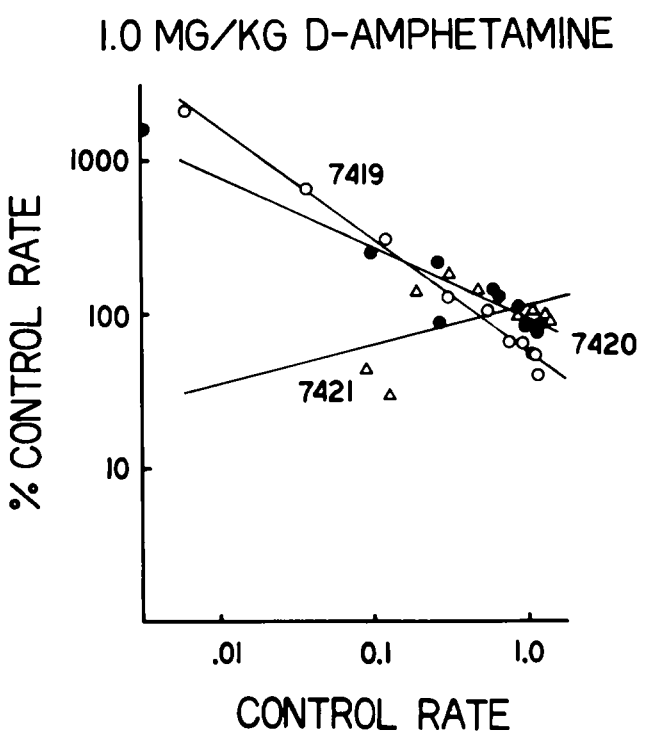

FIG. 2. The effect on response rates in each tenth of an FI-3 min schedule of introducing injections of 1.0 mg/kg d-amphetamine 30 min prior to the session. Each point represents the mean of the first 2 sessions on d-amphetamine, calculated as a percentage of the corresponding mean rate for the 2 sessions before amphetamine was introduced. ○ : 7419; ● : 7420; △ : 7421.

showed rate dependent effects when changed from saline to d-amphetamine, and McKim (1973) found rate dependent effects in only 7 of 9 rats given 3.2 mg/kg scopolamine. Add to this the difficulty of producing a consistent drug state by repeated IP administration, and the inconsistency of the rate dependent effect of the drug-to-saline change is understandable.

Since rate dependent effects can be produced by changing from saline to drug, from drug to saline, and by irrelevant changes in the stimulus situation [15], it may be that all these effects are a result of changes in the stimulus situation. It would be interesting to examine what these rate dependent changes mean in terms of the experimental control of behavior.

Let us use the example of a single drug injection producing rate dependent effects. Suppose that the experimental contingencies generate a variety of response rates under control conditions. Any demonstration of stimulus control or schedule control over responding must, by definition, involve differences in response rate or probability, so most experimental paradigms of interest will produce different rates. If the effect of a drug is to eliminate those previous differences and make all rates the same, then the degree and direction of change in rate will depend completely on the predrug rate. Figure 4 provides a simple proof of this statement showing that a complete elimination of differences in response rate produces a perfect rate dependency and a regression line with a slope of −1 on the coordinates shown. To the extent that the drug merely reduces, rather than eliminates, differences in drug effect, the slope would not be so steep. It should be

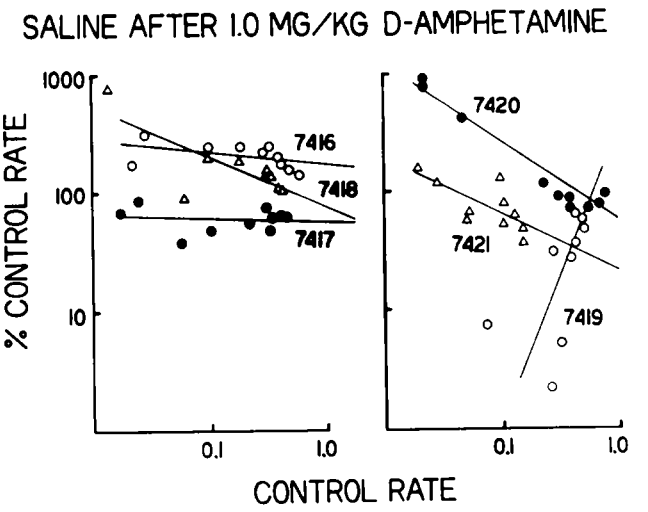

FIG. 3. The effect on response rates in each tenth of an FI-3 min schedule of introducing saline injections prior to the session after 22 or 24 sessions with d-amphetamine. Calculations were the same as in Fig. 2. ○ : 7416, 7419; ● : 7417, 7420; △ : 7418, 7421.

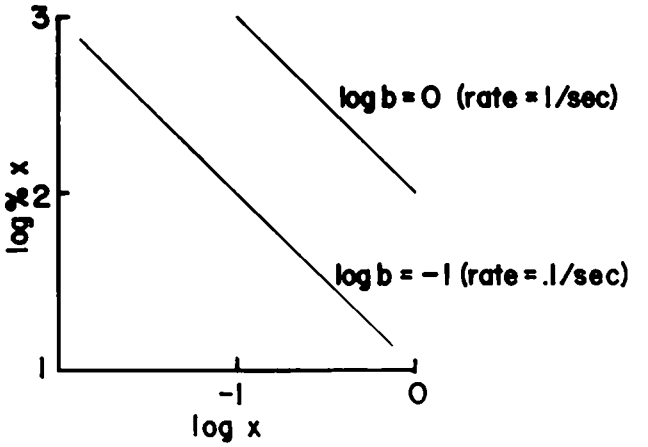

FIG. 4. Proof that a constant response rate, calculated as a percentage of variable response rates, produces a perfect rate dependency. Let x = predrug rate (variable); let b = rate after drug (constant); then: % predrug rate = b/x · 100; log % predrug rate = −logx + logb + 2.

pointed out that the different predrug rates may be generated in any order; as long as less variable postdrug rates are calculated as percentages of more variable predrug rates, the rate dependent effect will be seen. In other words, any loss in stimulus control or in schedule control of behavior may be seen as a rate dependent effect. Such losses in control may be obtained by altering the stimulus situation ([13], pp. 163–164). The losses in control produced by stimulus change would be expected to be greater for behaviors under fairly weak control and less for strongly-controlled behaviors, a phenomenon also found with drug induced decreases in control [6] and with rate dependent effects on FI performance [8]. It therefore seems quite possible that rate dependent drug effects on FI performance are a result of drug induced changes in the stimulus environment of the animal, producing some loss of control by the FI schedule.

REFERENCES

1. Dews, P. B. A behavioral effect of amobarbital. *Arch. exp. Path. Pharmak.* **248:** 296–307, 1964.
2. Flanagan, B. and W. B. Webb. Disinhibition and internal inhibition in fixed interval operant conditioning. *Psychon. Sci.* **1:** 123–124, 1964.
3. Frankenheim, J. M., D. E. McMillan and L. S. Harris. Effects of 1^{-9}- and 1^{-8}-trans-tetrahydrocannabinol and cannabinol on schedule-controlled behavior of pigeons and rats. *J. Pharmac. exp. Ther.* **178:** 241–252, 1971.
4. Hinrichs, J. V. Disinhibition of delay in fixed-interval instrumental conditioning. *Psychon. Sci.* **12:** 313–314, 1968.
5. Kelleher, R. T. and W. H. Morse. Determinants of the specificity of the behavioral effects of drugs. *Ergebn. Physiol.* **60:** 1–56, 1968.
6. Ksir, C. Scopolamine and amphetamine effects on discrimination: Interaction with stimulus control. *Psychopharmacologia* **43:** 37–41, 1975.
7. Ksir, C. and R. Pope. An inexpensive minicomputer system for controlling behavior experiments with animals. *Behav. Res. Meth. Instrument.* **7:** 325–326, 1975.
8. McKearney, J. W. Rate-dependent effects of drugs: Modification by discriminative stimuli of the effects of amobarbital on schedule-controlled behavior. *J. exp. Analysis Behav.* **14:** 167–175, 1970.
9. McKim, W. A. The effects of scopolamine on fixed-interval behaviour in the rat: A rate-dependency effect. *Psychopharmacologia* **32:** 255–264, 1973.
10. McMillan, D. E. The effects of sympathomimetic amines on schedule-controlled behavior in the pigeon. *J. Pharmac. exp. Ther.* **160:** 315–325, 1968.
11. McMillan, D. E. Drugs and punished responding I: Rate-dependent effects under multiple schedules. *J. exp. Analysis Behav.* **19:** 133–145, 1973.
12. Stitzer, M., J. Morrison and E. F. Domino. Effects of nicotine on fixed interval behavior and their modification by cholinergic agonists. *J. Pharmacol. exp. Ther.* **171:** 166–177, 1970.
13. Sutherland, N. S. and N. J. Mackintosh. *Mechanisms of Animal Discrimination Learning.* New York, Academic Press, 1971.
14. Tilson, H. A. and S. B. Sparber. Similarities and differences between mescaline, lysergic acid diethylamide-25 (LSD) and d-amphetamine on various components of fixed-interval responding in the rat. *J. Pharmacol. exp. Ther.* **184:** 376–384, 1973.
15. Wilkie, D. M. Stimulus control of responding during a fixed-interval reinforcement schedule. *J. exp. Analysis Behav.* **21:** 425–432, 1974.