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A PARAMETRIC EVALUATION OF THE HEDONIC AND MOTORIC EFFECTS OF DRUGS: PIMOZIDE AND AMPHETAMINE

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This study uses a curve-fitting approach to evaluate the effects of drugs on reinforced responding in rats. The subjects obtained reinforcement according to a series of five different variable-interval schedules (a five-component multiple schedule). For each rat, pimozide, a neuroleptic, decreased response rate, and the decrease was associated with (1) a decrease in the estimated asymptotic response rate and (2) an increase in the rate of reinforcement necessary for half-asymptotic responding. That is, pimozide decreased the proportion of responding maintained by a given rate of reinforcement. In contrast, intermediate doses of amphetamine increased response rate and increased the proportion of responding maintained by a given rate of reinforcement. It was proposed that the response rate asymptote indexes motor capacity, and the rate of reinforcement necessary for half-asymptotic responding indexes reinforcement efficacy; accordingly, pimozide decreased motor capacity and reinforcement strength and amphetamine increased reinforcement strength.

Key words: reinforcement strength, motor capacity, drugs, pimozide, amphetamine, matching law, variable-interval schedules, lever pressing, rats

Neuroleptics typically decrease reinforced responding. One interpretation is that the drug reduces the subject's sensitivity to normally reinforcing stimuli, such as food or water. For example, Wise, Spindler, deWit, and Gerber (1978) wrote, "neuroleptics appear to take the pleasure out of normally rewarding brain stimulation, take the euphoria out of normally rewarding amphetamine, and take the 'goodness' out of normally rewarding food." Those favoring this view call the result neuroleptic-induced anhedonia (e.g., Wise et al., 1978). Others, however, have suggested that neuroleptic-induced response depression is due to a motor deficit (e.g., Tombaugh, Tombaugh, & Anisman, 1979). Recently, Ettenberg, Koob, and Bloom (1981) used the following test to distinguish between the two interpretations. They compared the effects of alpha-flupenthixol on two different responses in rats: lever pressing for rewarding brain stimulation and nose poking for rewarding brain stimulation. The results varied with the response requirement: alpha-flupenthixol greatly reduced lever pressing but only moderately reduced nose poking. Ettenberg et al. contend that since the rats continued to nose poke for brain stimulation, the neuroleptic did not produce anhedonia. But this interpretation overlooks the possibility that the neuroleptic may have partially blunted the reinforcing strength of brain stimulation. Perhaps nose poking is normally maintained by a lower level of reward than lever pressing, and thus lever pressing extinguished whereas nose poking persisted. The problem is that the criterion for reinforcement strength is ambiguous. Wise et al. and Ettenberg et al. used change in absolute response rate to define change in susceptibility to reinforcement, yet both the motoric and hedonic interpretations predict similar modifications of absolute response level.

Faced with the ambiguity that attends absolute response-rate measures of reinforcement efficacy, some researchers have used changes in relative response rate (e.g., Griffiths, Wurster, & Brady, 1981; Johanson & Schuster, 1975). Their argument is that relative changes are independent of possible motor deficits. A similar logic can be applied to the parameters of the matching equation (Herrnstein, 1974). This equation, describing a rectangular hy-

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perbola, states that response rate is a negatively accelerated function of reinforcement rate:

$$B = \frac{kR}{R + R_e}, \quad (1)$$

where B is response rate (e.g., lever presses per min), R is reinforcement rate (e.g., pellets per hour), and k and R_e are constants, estimated from the data. These constants have been the subject of both theoretical and empirical studies (e.g., see de Villiers & Herrnstein, 1976; Herrnstein, 1974), but have figured in only a few psychopharmacology studies (e.g., Bradshaw, Ruddle, & Szabadi, 1981; Heyman & Coons, Note 1). In the experiment described below, k and R_e are used to evaluate the effects of a neuroleptic and neuroleptic antagonist.

It is proposed that changes in the parameter k measure changes in motor capacity. This proposal is supported by the finding that changes in the response requirement change k (e.g., Herrnstein, 1974; McSweeney, 1978). For example, McSweeney showed that shifting pigeons from a key-peck requirement to a treadle-kick requirement shifted k from about 55 responses per minute to about 18 responses per minute. Moreover, the change in the manipulandum had no systematic effect on R_e.

It is proposed that changes in the parameter R_e measure changes in reinforcement efficacy. This proposal is supported by several studies and is consistent with the mathematical relation that the magnitude of R_e is equal to the reinforcement rate that maintains half-maximal responding (note, $B = k/2$ if $R = R_e$). For example, in a study with rats, Guttman (1954) used two different concentrations of sucrose to reinforce lever pressing. The higher concentration (which humans would call sweeter) decreased R_e but did not change k (see de Villiers & Herrnstein, 1976). This means that a given rate of the higher concentration maintained a larger proportion of asymptotic responding, or, in terms of reinforcement strength, increasing concentration increased efficacy. Note that the two studies (McSweeney, 1978, and Guttman, 1954) showed that it is possible to arrange conditions that change only one of the parameters of Equation 1 (of course there may be treatments that change both parameters).

Experiment 1 tested the effects of pimozide, a neuroleptic, on k and R_e. Since this drug typically depresses reinforced responding, the two simplest outcomes are a decrease in k (a pure motor deficit) or an increase in R_e (a pure reward deficit). Experiment 2 tested the effects of amphetamine on k and R_e. Amphetamine is classified as a stimulant (e.g., Iversen & Iversen, 1981), and a number of its effects are opposite to those of pimozide. At intermediate doses it increases response rate, and according to biochemical studies, amphetamine increases the availability of dopamine at brain receptor sites, whereas pimozide decreases the availability of dopamine at these sites (e.g., see Creese, Burt, & Snyder, 1978; Moore, 1978). For intermediate doses of amphetamine, then, the simplest outcome is either an increase in k or a decrease in R_e.

METHOD

Subjects

Seven experimentally naive male albino rats served (Charles River Breeders, CD strain), four in Experiment 1 and three in Experiment 2. The rats were about 6 months old, weighed between 530 and 680 g prior to food deprivation, and for the course of the study were maintained at either 80% (Experiment 1) or 75% (Experiment 2) free-feeding weight. (Other research [Heyman & Seiden, Note 2] has shown that this weight difference had no apparent influence on the drug effects.)

Apparatus

The experiments were conducted in a standard, single-lever, operant conditioning chamber (20.5 cm by 23.5 cm by 19.5 cm). The response lever was approximately 6.5 cm from the floor on the left side of the front panel and was operated by a force of more than .15 N. Stimulus conditions were set by a buzzer (Sonalert) and a light. An opening, 5 cm to the right of the lever, provided access to a small (.10 ml) dipper of milk. The dipper was operated by a solenoid, and the milk was made from a powder mix (Carnation, 3 parts water to 1 part powder, with one tablespoon of sugar per quart.) The buzzer, chamber lights, and dipper were controlled by a PDP 8-e computer, and the chamber was protected from extraneous sounds by a large, insulated, wooden box.

Procedure

Each session consisted of a series of five variable-interval (VI) reinforcement schedules (a

five-component multiple schedule). Each schedule was available for 500 sec, and a 500-sec timeout period separated consecutive schedules. The programmed interreinforcement intervals approximated an exponential distribution (Fleshler & Hoffman, 1962), and the mean times for the five distributions were 160 sec, 80 sec, 40 sec, 20 sec, and 10 sec. Reinforcement consisted of 3.5-sec access to the dipper, and during this time the VI timer and session clock did not run. In Experiment 1 the order of the schedules was from VI 160-sec (the leanest) to VI 10-sec (the densest), and in Experiment 2 the order was lean to rich for two rats (Rats 902 and 904) and from rich to lean for one rat (Rat 906). The buzzer set the stimulus conditions for the different reinforcement rates. The frequencies were 1/8 sec, 1/6 sec, 1/4 sec, 1/2 sec, and 1/1 sec, with frequency corresponding to reinforcement density. During the timeout, the chamber lights and buzzer were off and responses had no experimentally arranged consequences (although they were recorded).

Drugs

Pimozide was injected intraperitoneally approximately 4 hours prior to testing. Each rat received three different doses in irregular order, .2, .3, and .6 mg/kg, and each dose was administered on three occasions. The pimozide was dissolved in 10 ml of distilled water with tartaric acid (approximately 7 parts acid to 1 part pimozide) and brought to final solution with distilled water. The injection volume was 1 ml.

d-Amphetamine was injected intraperitoneally approximately 20 min before the session. Each rat received vehicle (saline) and four concentrations: .25, .5, 1.0, and 2.0 mg/kg in irregular order. Each dose was administered three times.

The experiments were conducted 6 days a week at approximately the same time each day. Injections began after at least 15 sessions of training and at least 5 sessions with no systematic changes in k and R_e. In Experiment 1 there were 53, 56, 40, and 22 pre-injection sessions for Rats 21, 23, 24, and 901, respectively, and in Experiment 2 there were 21, 17, and 49 pre-injection sessions for Rats 902, 904, and 906. Once injections began, they were given about once a week and were restricted to at least 3 days since the last injection. Note that baseline and drug sessions alternated and that each rat served as its own control.

Statistics

The method of least squares was used to find the best-fitting values of k and R_e. Since Equation 1 is nonlinear, the least-squares problem results in two nonlinear equations in k and R_e. Wetherington and Lucas (1980) have outlined the problem and described an efficient approximation technique for solving the nonlinear equations. The solutions are the best-fitting values of k and R_e to near machine accuracy. Note that Equation I was originally used as a description of experiments in which reinforcement rate varied between sessions (Herrnstein, 1970). In experiments 1 and 2, reinforcement rate varied within sessions. Nevertheless, Equation 1 described the results at least as well as typically found in the original application.

Changes in k and R_e were calibrated by standard deviation scores. For example, for one subject the .6 mg/kg dose of pimozide decreased k by about two standard deviations and increased R_e by about five standard deviations. The calculations for Rat 21 demonstrate how variability was measured. This rat amassed 84 sessions that followed a drug injection by at least 3 days. These 84 sessions were grouped into 28 three-session units so that the baseline and drug conditions represented similar amounts of behavior (recall that there were three injections at each dose level). For each three-session unit, a value of k and R_e was calculated, and the standard deviations were determined from these estimates. In Experiment 1 there were 28, 22, 19, and 18 three-session baseline units for Rats 21, 23, 24, and 901, respectively; and in Experiment 2 there were 27, 27, and 13 three-session baseline units for Rats 902, 904, and 906, respectively.

RESULTS

Experiment 1

Pimozide dose dependently decreased lever pressing. Figure 1 shows that the same overall pattern described each rat, and Table 1 shows that the percentage decreases in response rate were about the same for three of the rats (21, 23, and 24). For example, under the schedule with the highest reinforcement rate (VI 10-sec), this group showed decreases of approximately 30%, 55%, and 90% at the .2, .3, and .6 mg/kg

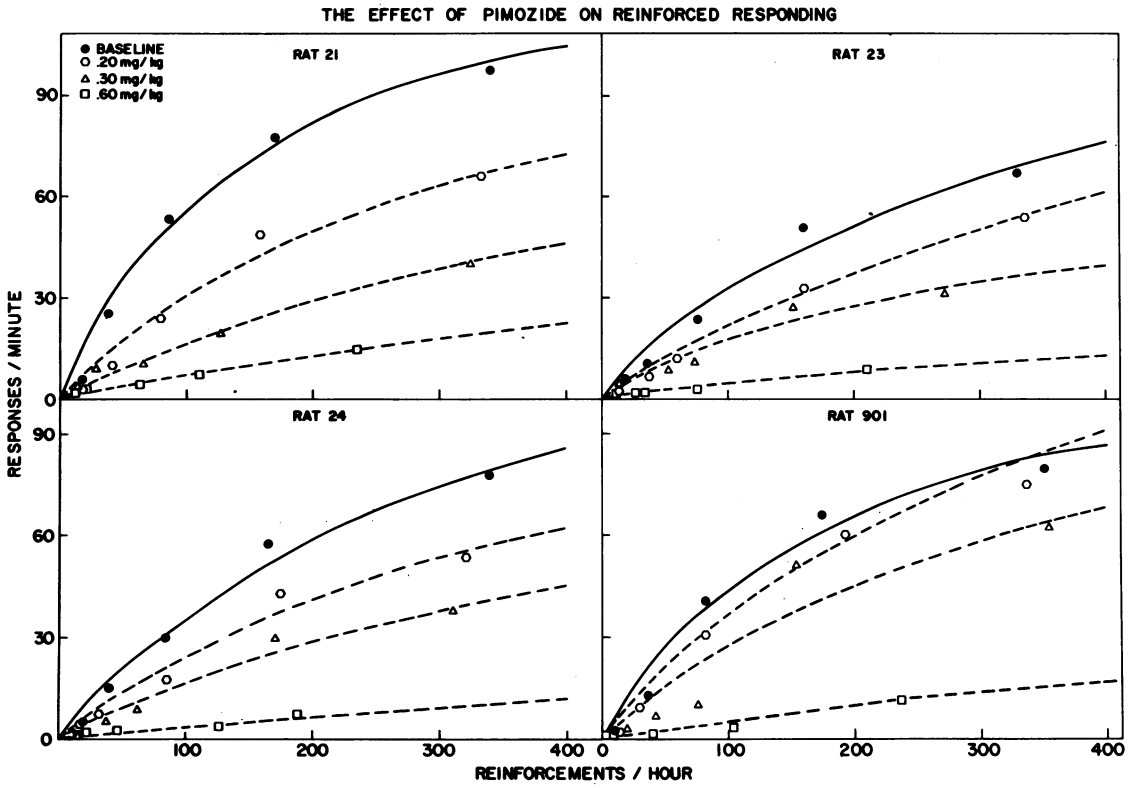

Fig. 1. The effect of pimozide on variable-interval schedule performance. The baseline rates were calculated from sessions that were not preceded by a drug injection. Sample sizes were 84 sessions, 66 sessions, 57 sessions, and 54 sessions for Rats 21, 23, 24, and 901, respectively. Drug response rates were averaged from three sessions for each dose level. The theoretical curves are the best-fitting rectangular hyperbolas. The parameter values, k, and R_e, are listed in Table 2.

doses. For Rat 901, pimozide produced smaller decreases but in the same dose-dependent pattern.

Table 2 shows that response rate decreases were accompanied by dose-dependent increases in R_e. The average increments were 1.6, 2.4, and 9.5 standard deviation units for the .2, .3, and .6 mg/kg doses, respectively. For example, for Rat 901 the baseline estimate of R_e for nondrug responding was 206 reinforcers an hour, whereas with the .3 mg/kg dose of pimozide, R_e was 467 reinforcers an hour. In other words, with pimozide, the rat needed about twice as many reinforcers to maintain its half-maximal response rate.

Pimozide produced smaller changes in k than in R_e. The lowest dose, .2 mg/kg, did not appear to have a significant effect on k. There were both increases and decreases, with an average change of .25 standard deviations. The .3 mg/kg dose decreased k in three rats (Rat 901 was the exception), and the .6 mg/kg dose decreased k in every subject, with an average decrement of 1.7 standard deviations. For example, the estimated asymptotic response rate for Rat 23 in baseline was 141 responses per minute, whereas with the .3 mg/kg dose it was 66 responses per minute. To summarize, then, pimozide dose dependently increased R_e and decreased k, and these two changes are cooperative in the sense that each is associated with a reduction in response rate.

Experiment 2

There was a bitonic relationship between amphetamine dose and change in response rate. Figure 2 and Table 3 show that the intermediate doses, .25 to 1.0 mg/kg, increased bar pressing, whereas the highest dose, 2.0 mg/kg, decreased or eliminated responding. Each rat showed this bitonic pattern, and Figure 2 and Table 3 indicate that the .25 and 1.0 mg/

Table 1

Summary of absolute reinforcement and response rates for pimozide experiment. The baseline data are the averages from sessions that occurred at least 3 days since the last pimozide injection. The sample sizes are 84, 66, 57, and 54 sessions for Rats 21, 23, 24, and 901, respectively. The pimozide rates are the averages from the three sessions at each dose level.

	VI 160-Sec		*VI 80-Sec*		*VI 40-Sec*		*VI 20-Sec*		*VI 10-Sec*	
Subject and Condition	*Reinf/ Hr*	*Resp/ Min*	*Reinf/ Hr*	*Resp/ Min*	*Reinf/ Hr*	*Resp/ Min*	*Reinf/ Hr*	*Resp/ Min*	*Reinf/ Hr*	*Resp/ Min*
RAT 21										
Baseline	17.5	5.9 ± 5.4	37.5	25.8 ± 10.3	84.9	53.5 ± 10.5	170.8	78.1 ± 10.7	340.6	98.1 ± 10.3
.2 mg/kg	17.2	2.9 ± .6	40.5	10.2 ± 1.5	79.3	23.9 ± 9.5	158.0	48.9 ± 2.9	333.0	66.4 ± 14.9
.3 mg/kg	17.3	2.4 ± .7	25.6	7.1 ± 1.8	65.3	9.7 ± 2.7	126.0	20.0 ± 5.3	324.0	40.4 ± 7.5
.6 mg/kg	19.8	2.8 ± 1.3	12.4	1.5 ± 1.7	62.0	4.0 ± 2.0	110.0	7.5 ± 6.0	234.0	15.0 ± 7.5
RAT 23										
Baseline	17.3	5.4 ± 1.6	36.6	10.5 ± 4.3	75.7	23.5 ± 8.8	160.7	50.4 ± 12.9	330.8	67.9 ± 9.9
.2 mg/kg	13.2	2.1 ± 1.2	38.0	6.6 ± 2.0	59.6	12.8 ± 4.5	161.0	33.0 ± 10.7	334.0	53.9 ± 3.8
.3 mg/kg	12.3	3.6 ± 2.8	32.6	8.1 ± 2.6	73.7	9.8 ± 3.9	151.6	26.7 ± 10.7	271.5	31.5 ± 11.7
.6 mg/kg	10.0	.7 ± .3	26.2	1.2 ± .9	33.4	2.0 ± .7	75.0	2.7 ± 8.6	209.0	8.0 ± 2.4
RAT 24										
Baseline	19.1	5.3 ± 6.0	39.3	15.6 ± 5.5	83.4	30.4 ± 11.6	165.7	57.7 ± 12.5	341.8	78.1 ± 4.7
.2 mg/kg	18.5	4.1 ± .3	26.4	7.5 ± 1.0	85.0	17.4 ± 1.2	176.0	43.0 ± 3.3	321.0	53.8 ± 10.3
.3 mg/kg	10.2	.9 ± 1.2	34.4	4.2 ± 1.5	54.3	7.2 ± 3.7	160.5	27.5 ± 4.4	310.5	37.8 ± 10.7
.6 mg/kg	14.7	1.10 ± .8	22.3	1.6 ± .4	46.0	2.5 ± 1.7	125.3	3.6 ± 2.4	187.0	7.2 ± 1.1
RAT 901										
Baseline	13.9	2.5 ± 1.8	35.9	12.7 ± 7.0	82.7	40.5 ± 11.5	174.8	66.9 ± 8.7	349.3	80.3 ± 9.6
.2 mg/kg	14.7	1.8 ± .4	30.0	9.1 ± 6.5	82.0	31.0 ± 13.5	186.0	60.0 ± 10.1	337.0	82.0 ± 4.0
.3 mg/kg	19.4	3.8 ± .6	41.2	6.9 ± .1	76.2	10.6 ± 1.9	154.0	51.3 ± 10.4	353.0	62.0 ± 4.0
.6 mg/kg	3.7	.2 ± .2	7.3	.5 ± .1	42.0	1.5 ± .8	109.0	5.6 ± .7	212.0	9.9 ± 4.9

Table 2

Summary of the effects of pimozide on the two parameters of the hyperbolic response-rate equation: $B = kR/(R + R_e)$. Standard deviations for baseline sessions are from samples of three sessions each so that the units would be commensurable with drug session rates (see text).

Subject and Condition	*k Resp/min*	*Standard Deviation/ Change in Std. Dev.*	*R_e Reinf/hr*	*Standard Deviation/ Change in Std. Dev.*	*r^2*
RAT 21					
Baseline	149.3	19.7	167.0	68.5	.984
.2 mg/kg	143.8	−.3	368.4	+2.6	.976
.3 mg/kg	122.0	−1.4	654.3	+7.1	.993
.6 mg/kg	90.6	−3.0	1186.8	+14.9	.980
RAT 23					
Baseline	141.0	56.7	337.4	217.1	.984
.2 mg/kg	170.0	+.5	710.4	+1.7	.996
.3 mg/kg	66.2	−1.3	271.5	−.3	.950
.6 mg/kg	62.2	−1.4	1424.2	+5.0	.986
RAT 24					
Baseline	152.0	53.1	309.8	214.5	.988
.2 mg/kg	128.3	−.5	420.5	+.5	.975
.3 mg/kg	109.3	−.9	561.8	+1.2	.978
.6 mg/kg	34.6	−2.2	783.2	+2.2	.889
RAT 901					
Baseline	132.6	44.8	205.7	156.4	.969
.2 mg/kg	189.0	+1.3	428.0	+1.5	.999
.3 mg/kg	151.9	+.4	466.7	+1.6	.886
.6 mg/kg	130.3	−.05	2671.0	+15.8	.994

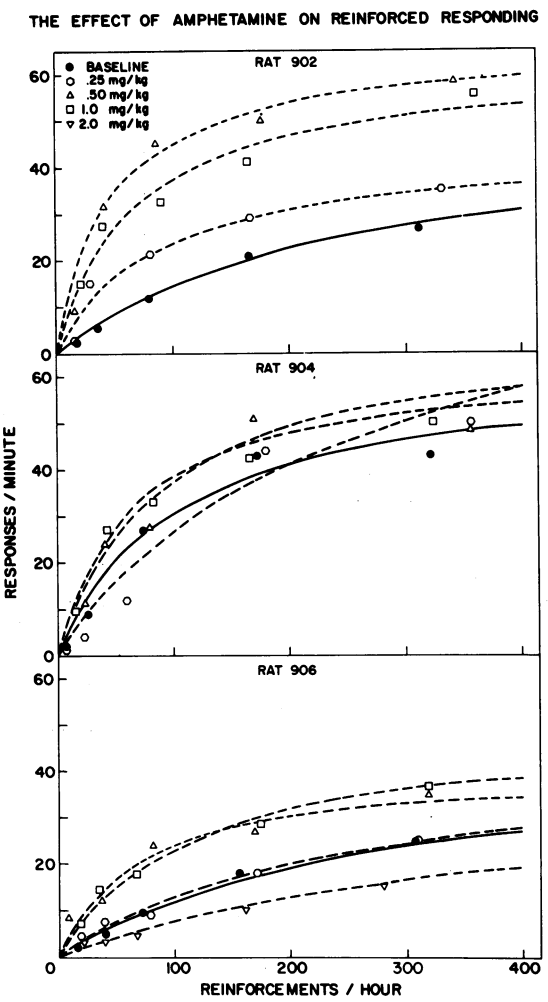

Fig. 2. The effect of amphetamine on variable-interval schedule performance. Sample sizes for baseline sessions were 51 sessions for Rats 902 and 903 and 39 sessions for Rat 904. For drug sessions the rates were averaged from three sessions. Table 4 lists the best-fitting parameter values. See Figure 1 and text for other details.

kg doses circumscribed the dose that would have produced the maximum increase. At the 2.0 mg/kg concentration, two of the rats stopped bar pressing. They were observed from time to time, and they appeared to spend most of the session handling the wood chips that lined the bottom of the chamber. (In contrast, when rats stopped responding under pimozide, they sat relatively motionless.) The one rat that continued to respond at the 2.0 mg/kg dose (906) also showed the smallest reaction to the .25 mg/kg dose.

Changes in response rate were accompanied by bitonic changes in R_e (see Table 4). For Rats 902 and 906, the .50 mg/kg dose produced the largest decrement in R_e, whereas the lower and higher doses produced somewhat smaller decrements. Rat 904 was idiosyncratic in that the .25 mg/kg dose produced an increase in R_e and the 1.0 mg/kg rather than the .50 mg/kg dose produced the largest decrement in R_e. For group results, Table 4 shows that the median decrements in R_e were .4, 1.9, and 1.8 standard deviation units for doses up to 1.0 mg/kg. At the 2.0 mg/kg dose, the one rat that continued to respond showed an increase in R_e, suggesting that higher doses of amphetamine may decrease the reinforcing power of milk (Heyman & Seiden, Note 2).

Amphetamine did not produce systematic nor large changes in k. Increases and decreases were about equally likely, so the average change was less than one standard deviation and showed no relationship to drug dose. Also recall that the order of reinforcement-rate presentation differed for Rat 906: It ran from rich to lean. This difference appears not to have influenced the amphetamine effect on the parameters of Equation 1; for each rat there were bitonic changes in R_e and little change in k.

DISCUSSION

According to the proposition that k measures motor capacity and R_e measures reinforcement effectiveness, Experiments 1 and 2 support the following conclusions: Pimozide reduced the rats' susceptibility to the reinforcing properties of milk, and to a lesser degree, it decreased the rats' ability to press the lever. That is, pimozide interfered with both hedonic and motoric processes. In contrast, intermediate doses of amphetamine increased susceptibility to the reinforcing properties of milk and did so without systematically changing the motor capacity parameter. These results support the anhedonia interpretation of neuroleptic-induced response depression, but with the qualification that neuroleptics may simultaneously change hedonic and motoric components of operant responding.

The results from Experiments 1 and 2 are compatible with a number of previous studies. Zarevics and Setler (1979) investigated the influence of amphetamine and pimozide on the minimum level of brain stimulation that would maintain lever pressing. Amphetamine lowered the threshold, which is analogous to

Table 3

Summary of absolute reinforcement and response rates for amphetamine experiment. The format is the same as in Table 1.

Subject and Condition	VI 160-Sec		VI 80-Sec		VI 40-Sec		VI 20-Sec		VI 10-Sec	
	Reinf/ Hr	Resp/ Min	Reinf/ Hr	Resp/ Min	Reinf/ Hr	Resp/ Min	Reinf/ Hr	Resp/ Min	Reinf/ Hr	Resp/ Min
RAT 902										
Baseline	18.1	2.2 ± .5	35.5	5.2 ± 2.6	81.0	11.5 ± 3.7	166.0	21.0 ± 3.0	316.0	26.6 ± 3.5
0.0 mg/kg	22.3	2.0 ± 2.5	30.0	3.7 ± 3.2	76.3	13.2 ± 3.6	165.6	20.4 ± 5.3	340.0	27.2 ± 4.2
0.25 mg/kg	17.2	2.9 ± 1.5	30.0	15.0 ± 3.6	82.4	21.0 ± 9.2	168.4	28.3 ± .2	332.9	34.9 ± 5.8
0.50 mg/kg	16.3	8.9 ± 6.7	29.4	31.4 ± 6.8	86.2	45.4 ± 6.9	177.4	50.1 ± 6.0	342.8	58.3 ± 10.8
1.0 mg/kg	19.9	14.5 ± 3.7	40.4	27.1 ± 4.3	91.2	32.4 ± 3.9	158.4	41.1 ± 3.7	349.9	54.8 ± 3.4
2.0 mg/kg	—				—		—		—	
RAT 904										
Baseline	8.0	2.0 ± 1.4	26.0	9.1 ± 4.4	74.0	26.6 ± 7.0	173.0	43.0 ± 5.1	321.0	43.4 ± 4.1
0.0 mg/kg	17.0	2.5 ± .7	23.0	5.3 ± 3.1	83.3	21.5 ± 5.1	172.0	41.2 ± 4.6	317.0	44.0 ± 3.7
0.25 mg/kg	7.0	1.0 ± 8.8	22.0	3.5 ± 6.7	49.0	12.0 ± 10.3	179.0	44.0 ± 2.9	330.0	48.0 ± 1.5
0.50 mg/kg	22.0	11.0 ± 4.9	43.0	24.0 ± 2.7	82.0	38.0 ± 14.1	109.0	51.0 ± 12.4	330.0	49.5 ± 4.3
1.0 mg/kg	14.6	9.3 ± 8.2	32.6	27.0 ± 20.1	82.3	33.3 ± 13.7	164.8	42.1 ± 9.3	325.4	49.5 ± 4.3
2.0 mg/kg	—				—		—		—	
RAT 906										
Baseline	16.4	1.7 ± .5	28.9	4.7 ± 1.4	72.9	9.1 ± 2.2	156.0	17.8 ± 3.3	308.4	25.0 ± 2.2
0.0 mg/kg	27.3	2.8 ± 1.2	29.9	5.2 ± 2.3	79.3	10.2 ± 1.9	155.0	21.0 ± 4.8	311.7	24.0 ± 1.0
0.25 mg/kg	20.0	4.6 ± 2.7	30.0	7.4 ± 3.6	80.0	8.9 ± 5.3	172.0	18.0 ± 4.2	309.0	25.3 ± .8
0.50 mg/kg	9.8	8.3 ± 4.9	37.8	11.6 ± 1.4	91.0	24.0 ± 14.8	169.0	26.8 ± 5.0	324.9	34.4 ± 1.0
1.0 mg/kg	17.2	7.3 ± 3.2	35.1	14.4 ± 6.3	68.2	18.2 ± 9.0	175.3	28.4 ± 10.5	319.0	35.5 ± 7.7
2.0 mg/kg	29.9	3.0 ± 1.4	22.2	3.1 ± .9	68.5	3.7 ± 3.8	132.0	9.7 ± 1.7	271.6	15.1 ± 5.7

Table 4

Summary of the effects of amphetamine on the two parameters of the hyperbolic response rate equation. The format is the same as in Table 2.

Subject and Condition	k Resp/min	Standard Deviation/ Change in Std. Dev.	R_e Reinf/hr	Standard Deviation/ Change in Std. Dev.	r^2
RAT 902					
Baseline	49.6	8.1	258.6	89.6	.989
0 mg/kg	45.7	−.5	224.9	−.4	.977
.25 mg/kg	44.1	−.7	87.7	−1.9	.946
.50 mg/kg	66.1	+2.0	46.6	−2.4	.924
1.0 mg/kg	62.6	+1.6	68.8	−2.1	.957
2.0 mg/kg	—	—	—	—	—
RAT 904					
Baseline	60.7	12.5	100.6	50.1	.965
0 mg/kg	73.1	+1.0	175.3	+1.5	.939
.25 mg/kg	94.4	+2.7	261.3	+3.2	.970
.50 mg/kg	63.2	+.2	65.5	−.7	.924
1.0 mg/kg	55.8	−.4	48.7	−1.0	.959
2.0 mg/kg	—	—	—	—	—
RAT 906					
Baseline	50.2	10.2	304.2	121.6	.995
0 mg/kg	45.8	−.4	236.3	−.6	.961
.25 mg/kg	45.1	−.5	251.1	−.4	.957
.50 mg/kg	41.3	−.9	75.4	−1.9	.951
1.0 mg/kg	44.1	−.6	87.3	−1.8	.988
2.0 mg/kg	41.5	−.9	471.4	+1.4	.960

a decrease in R_e, and pimozide increased the threshold, which is analogous to an increase in R_e. Bradshaw et al. (1981) described the effects of .3 and .6 mg/kg of amphetamine on k and R_e in rats responding for food pellets. They injected their subjects twice a week for approximately 14 months. Amphetamine dose dependently decreased R_e, as in Experiment 2. However, there was also a dose-dependent decrease in k, whereas Experiment 2 showed no systematic changes in this parameter. The source of this difference is not clear because the drug administration regimes of the two studies differed widely.

The research described above supports the hypothesis that amphetamine and pimozide produced opposite changes in the parameter R_e. There is, however, a possible confound. In Experiment 1 reinforcement rate increased with successive schedule components so that there was a correlation between reinforcement rate and time since injection. Some of the relevant findings are: Using a variety of behavioral tests, Janssen and his colleagues (1968) established a temporal profile for pimozide. For most measures, the graphs show a relatively stable behavioral reaction for about 4 to 6 hours, beginning about 2 to 4 hours from injection. (Indeed, the initial interest in pimozide was due to its enduring effects.) In Experiment 2 schedule order was from lean to rich for two rats (902 and 904) but from rich to lean for the third (906). For each subject the .25 mg/kg to 1.0 mg/kg doses of amphetamine increased response rate, and there were no differences in performance that appeared to be related to schedule order. In addition, research currently in progress indicates that schedule order had no measurable influence on the results presented here.

In this paper the effects of drugs on response rate have been described in terms of the parameters of Equation 1. In contrast, in psychopharmacology the tradition has been to describe drug-induced changes in response rate in terms of the baseline response rate (e.g., Dews, 1958; Dews & Wenger, 1977). According to reviews (e.g., Dews & Wenger, 1977; Robbins, 1981), the basic findings were that drugs change lower baseline response rates more than higher baseline rates and that a straight line accurately describes the relationship between the logarithms of the drug response rates and the logarithms of the baseline response rates. (In these graphs, the experimenter plotted the ratio of the drug to baseline response rate on the y axis and the baseline response rate on the x axis.) Although this approach, called rate dependency, does not provide the logical structure for distinguishing between reinforcement and motor effects, it may be of interest to establish whether Equation 1 or rate dependency provides the better description of how drugs change response rate.

Dews and Wenger (1977) propose that the proper test of the rate-dependency hypothesis for amphetamine is that the relationship between the logarithms of the drug response rates and the logarithms of the baseline response rates be "sensibly linear with a negative slope." For example, a slope of 0.0 implies that all baseline rates are changed by the same proportion, and a positive slope implies either that higher rates are increased more than lower rates or that higher rates are decreased less than lower rates. Dews and Wenger restrict their quantitative prediction to amphetamine. However, extending their approach to pimozide, the simplest prediction is that decreases in response rate should correspond to a graph that is "sensibly linear" with a positive slope.

Equation 1 predicts that the ratios of drug to baseline response rates should take the form:

$$\frac{R_D}{R_C}=\frac{k'R/(R+R_e')}{k\,R/(R+R_e)}=\frac{k'(R+R_e)}{k\,(R+R_e')}, \quad (2)$$

where k' and R_e' are the drug condition parameters. When Equation 2 is plotted as a function of baseline response rates in logarithmic coordinates, the following relationships hold: If the drug changed k but not R_e, then drug response rates are a constant proportion of baseline response rates, and Equation 2 reduces to k'/k. In terms of the rate-dependency coordinates, this translates as a linear fit with a slope of 0.0 and an intercept of k'/k. If the drug changed only R_e or R_e and k, then the ratio between drug and baseline response rates depends on the magnitude of the reinforcement rate relative to the magnitude of R_e. For the range of reinforcement rates used in Experiments 1 and 2 and in the study of Bradshaw et al. (1981), the logarithms of Equation 2 appear to change linearly with the logarithms of the baseline response rates. Consequently, for the available published data, Equations 1 and 2 and the rate dependency yield equally

good descriptions of the results (see Bradshaw et al., 1981, Figure 3). However, for reinforcement rates that are large relative to R_e, Equations 1 and 2 predict that the x coordinate of the rate-dependency graph should approach the constant log (k) and that the y coordinate should approach the constant log (k'/k). Since the ratio more rapidly approaches its asymptotic value, the slope of the rate-dependency relation is curvilinear for response rates associated with high reinforcement rates. Heyman and Seiden (Note 2) tested this prediction in an experiment that provided a range of reinforcement rates that approximately doubled those used in Experiments 1 and 2. In general the results were consistent with the predictions of Equation 1 and consequently failed Dews and Wenger's (1977) test: The ratios of the drug and baseline response rates approached a constant value and the rate dependency relation was curvilinear.

In the introduction it was proposed that k measures motor capacity and that R_e measures reinforcement effectiveness. Whether or not these definitions prove useful is an empirical question. Possibly further research will show that k and R_e do not lead to a systematic account of drug-induced changes in reinforcement efficacy. However, results from Experiments 1 and 2 and elsewhere (e.g., McSweeney, 1978) are promising; they show that environmental and physiological manipulations produce systematic and predictable changes in k and R_e.

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