THE INFLUENCE OF *dl*-, *d*-, AND *l*-AMPHETAMINE AND *d*-METHAMPHETAMINE ON A FIXED-RATIO SCHEDULE

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In 1910, a systematic pharmacological investigation of a series of aliphatic and aromatic amines (Barger & Dale, 1910) revealed a number of compounds that had properties similar to those of epinephrine. These compounds elicited physiological responses of varying degree similar to functional stimulation of the sympathetic nervous system. From this work the term sympathomimetic amine was coined. Prior to this (in the 1880's), ephedrine, the active principle of the Chinese herb Ma Huang, had been studied and was discarded as being too toxic. Upon reinvestigation by Chen and Schmidt (1924), the pharmacological importance of ephedrine as a sympathomimetic was recognized. Publication of this work stimulated new interest in these amine compounds, especially the phenylethylamines and the phenylisopropylamines, the chemical nucleus structures of epinephrine and ephedrine, respectively.

phenylethylamine

phenylisopropylamine
(amphetamine)

epinephrine

ephedrine

desoxyephedrine
(methamphetamine)

Amphetamine was first described (Pines et al., 1930) as inducing a marked rise in blood pressure in man and dogs with drying of their mouths. Another report (Alles, 1933) noted that the compound increased respiration and caused awakening of lightly anesthetized animals. These effects were considered to be a result of stimulation of the central nervous system rather than of increased blood circulation. Subsequently, other investigators (Ehrich & Krumbhaar, 1937) reported that with the administration of large doses of amphetamine, normal growth of young rats was retarded by decreasing food intake. Clinically, Nathanson (1937) observed that patients taking this drug for other purposes showed a "loss of appetite" (inferred from reduced food consumption), with definite reduction in body weight. Another study, comparing amphetamine with ephedrine (Bahnsen et al., 1938), showed that amphetamine produced marked "appetite loss" (derived from subjective reports), whereas ephedrine appeared to have little of this effect.

Physically, amphetamine is a mixture of equal parts of optically active isomers, *d*-amphetamine and *l*-amphetamine. The mixture is referred to as *dl*-amphetamine.

Pharmacologically, these three compounds have been found qualitatively similar in their actions but different in potency. For example, *d*-amphetamine was reported (Prinzmetal & Alles, 1940) to be 1.5–2 times as potent as the *dl*-amphetamine and 3–4 times as potent as the *l*-isomer on the central nervous system (verbal reports). Otherwise, the three compounds were about equipotent in peripheral effects (blood pressure and heart rate) in human subjects. Another investigator (Rosenberg, 1940), using *dl*-amphetamine and *d*-amphetamine in obese patients, observed that the chief advantage of the latter compound was its greater central activity: "... it overcomes both the depression and the craving for food which are so typical of obstinate cases of obesity," without increase in other untoward side actions

The compound *d*-methamphetamine was described as having activity similar to that of amphetamine (Hauschild, 1938), with an enhanced effect on the central nervous system, i.e., wakefulness and euphoria with less intense undesirable side effects. Subjective studies in man (Jacobsen, 1938, 1939), comparing a series of sympathomimetic amines, found *dl*-methamphetamine somewhat less active than *dl*-amphetamine in "appetite depression" and about equal in other effects. However, Jacobsen reported that in small animals the *dl*-methamphetamine appeared to be the more active compound.

The drug action which facilitates the weight loss has been attributed to a variety of mechanisms (Harris et al., 1947), e.g., delayed stomach-emptying time, suppression of gastric secretions, diuresis, increased metabolic rate, increased motor activity, or decrease of "the desire or appetite for food." A comprehensive study by Harris et al. (1947) of *dl*-amphetamine- and *d*-amphetamine-induced weight losses indicated that these agents act primarily on the central nervous system on either a cerebral or hypothalamic level to induce a decrease in food intake. Other mechanisms which might be influenced by the drugs were considered as secondary factors which could contribute to the phenomena.

An appeal to "increased motor activity" or a "decrease in appetite" as possible explanations for the observed weight losses correlated with the administration of these compounds can be justified only on the basis of behavioral data. Whereas the appeal to "increased motor activity" refers to an easily observed datum, any explanation in terms of loss of appetite, hunger, or desire for food is inferred from the observation that the subjects ate less.

The first series of experiments to go beyond simple observations of food intake were the studies of Skinner and Heron (1937) and of Wentink (1938). Wentink showed that 15 minutes after doses of *dl*-amphetamine, rats on a fixed-interval (FI) schedule increased their lever-pressing behavior but decreased their food consumption. Skinner and Heron demonstrated that rats trained on FI schedules showed typical depressed curves after daily sessions of extinction runs. On the fourth day of extinction, caffeine, and on the eleventh day *dl*-amphetamine, induced responding rates almost equal to pre-extinction rates. These drugs therefore were thought to cause an organism to release energy at a higher rate than normal whether or not eating behavior was inhibited.

Dews (1956) reported that methamphetamine and pentobarbital more readily disturbed the fixed-interval (FI) than the fixed-ratio (FR) performance on multiple FI FR schedules. Morse and Herrnstein (1956) have shown that with appropriate low ratios on FR schedules, pigeons maintained stable base lines of performance over extended experimental sessions.

However, as the value of the ratio was increased, pausing after reinforcement occurred more frequently; and the duration of these pauses increased until at high enough ratios, responding ceased altogether. Lower response rates often occurred between the end of the pause and the resumption of the bird's regular high terminal rate before reinforcement. This phenomenon has been termed ratio strain (Morse & Herrnstein, 1956; Ferster & Skinner, 1957). Low doses (0.5 milligram) of methamphetamine decreased the duration of the pauses without appreciably affecting the response rate. A dose of 2 milligrams appeared virtually to eliminate the long pauses after reinforcement and to depress the running rate markedly. Dews (1958) has further shown that at optimal doses, methamphetamine, *d*-amphetamine, and pipradol increased the rate of responding of pigeons under schedules that require longer periods of time between reinforcements, e.g., FI 15 minutes or FR 900. With shorter schedules, VI 1 minute or FR 50, the rate increased only slightly. Recently, Kelleher and Cook (1959) reported that a wide range of doses of *d*-amphetamine depressed response rates of rats on an FR 50 schedule of food reinforcement.

The above data have shown that these compounds affect many different aspects of free-operant performance in different ways. Some of the effects depend on the kind of schedule used and the parameters specific to it (the length of an FI or the size of an FR). Furthermore, the performances in such procedures have been shown to be functions of the quality and quantity of reinforcement (Hutt, 1954).

The purpose of this study was to examine further the influence of *dl*-amphetamine sulfate, *d*-amphetamine sulfate, *l*-amphetamine phosphate, and *d*-methamphetamine hydrochloride in rats trained to obtain milk on a moderate FR schedule (30:1) which produced minimal or no straining.

METHOD

The subjects were eight male albino rats of a Wistar-derived strain, initially weighing 400–450 grams and deprived to 65–75% of their original body weight. They were trained on an FR 30. Each reinforcement consisted of 0.5 milliliter of a mixture of sweetened condensed milk, water, and Homicebrin (homogenized multiple vitamins, Eli Lilly and Company) in proportions of 1:1:0.01.

Two identical experimental cages were used in this study, each measuring 9 by 9 by 7.5 inches. The lever, a specially modified Switchcraft Lev-R No. 3002 (Verhave, 1958), was mounted 2 inches from the floor on one wall. It was adjusted to operate at approximately 10 grams of pressure through an excursion of approximately 0.25 millimeter. The reinforcement was delivered by a motor-driven dipper with a cup capacity of 0.5 milliliter. Illumination inside the cage was provided during a session by a single pilot light located in the wall above the lever. During the 8-second interval that the reinforcement was available to the rat, the light in the wall was switched off, and another pilot light illuminated the cup. At the end of a session the light over the lever was extinguished and a house light came on below the floor of the experimental cage. The cages were contained in light-proof, sound-resistant, ventilated boxes isolated from the control equipment.

The procedure was programmed on appropriate electrical and electronic timers and relay circuitry. The data were recorded on electrical impulse counters, running-time meters, and cumulative recorders.

The rats were given daily sessions of 40 reinforcements per session except on those days

when drugs were tested. At the completion of each session, each rat was given sufficient dry food to maintain the deprivation weight level. The drugs were dissolved in distilled water and administered subcutaneously. On days when drugs were given, each rat was run for 9–11 reinforcements prior to injection as a normal control period for that day. Following drug administration the rat was placed in a small observation cage for 30 minutes to allow the drug to be absorbed and take effect. (With *d*-methamphetamine, however, this time period was 20 minutes.) The animal was then returned to the experimental cage and permitted to obtain 40 reinforcements or until no responding had occurred for at least 60 minutes.

In addition to drug sessions, each rat was run several sessions with physiological saline. Other sessions were run in the same manner without drug to show changes in the curves when an unlimited number of reinforcements was available and satiation occurred.

RESULTS

Rat 82 (Fig. 1) showed an occasional pause following reinforcement and a response rate of 2.50 responses per second during regular 40-reinforcement control sessions. As this rat neared satiation, the rate slowed irregularly (Fig. 2), and the pauses between and after reinforcements lengthened. The three amphetamine drugs caused a general depression of the response rate. This depression appeared on the curves both as smooth, even slopes and as erratic, irregular slopes which were frequently interrupted by very brief pauses. These pauses even further depressed the over-all character of the curves. (See Fig. 2B for a detailed segment of such a curve.) At the two highest doses of *d*- and *l*-amphetamine, lever pressing temporarily stopped when the rat was returned to the cage after drug administration.

With *d*-methamphetamine at all three doses the rate declined. At 1 milligram per kilogram the decline in rate was even, with infrequent irregular segments. With the two higher doses, the rate was irregularly slowed, with definite pauses appearing during responding between reinforcements. At 3.2 milligrams per kilogram the rat completely ceased responding after 21 reinforcements.

Rat 84 (Fig. 3) had a normal rate¹ of about 2.55 responses per second and showed frequent very brief pauses after reinforcement. It approached satiation with a marked lengthening of every second or third pause with little or no slowing of the running rate. (See the segment of the satiation curve including the last 14 reinforcements.) The administration of the amphetamines induced only a slight depression of the response rate. The main effects were to increase the number and length of the pauses following reinforcement as well as to induce complete cessation of lever pressing for varying lengths of time prior to the return of responding. The size of the dose did not necessarily influence the duration of this initial pause. (See both the *d*- and the *l*-amphetamine data.) With *d*-methamphetamine the curves were the same as those with *d*- and *l*-amphetamine, except that the short pauses following reinforcement were not so apparent or frequent. Again, at the two higher doses the long delay before resumption of lever pressing appeared after drug administration. Also, with *dl*-amphetamine at 2 and 3.2 milligrams per kilogram and *d*-amphetamine and *d*-methamphetamine at 1 milligram per kilogram, this rat produced long pauses (7.5–10 minutes) after the first 14–26 reinforcements.

Rat 86 (Fig. 4), with a normal rate of about 3.2 responses per second, showed a 25-to-50-second pause after every fourth to eighth reinforcement. These pauses lengthened noticeably

¹Normal rate, hereafter in this report, refers to base-line performance determined as the mean response rate of 10 randomly selected daily sessions excluding immediate postdrug-day sessions.

RAT 82
FR-30 MILK

Figure 1. Cumulative records for Rat 82 under conditions noted.

when the animal approached satiation, and the rate then became slightly irregular. With *dl*-amphetamine, the rate was irregularly slowed, with marked pauses following reinforcement. (See Fig. 5B for detailed segment of curve showing irregular responding.) These two effects became accentuated with the higher doses used. At doses of 1 and 2 milligrams per kilogram of *d*-amphetamine the effects on rate and pausing were similar to those seen with *dl*-amphetamine. Complete suppression of bar pressing occurred for 103 and 214 minutes, respectively, on doses of 2 and 3.2 milligrams per kilogram of *d*-amphetamine. The return of responding on the higher dose was characterized by an almost normal rate for 25 reinforcements, when it abruptly became slowed with the appearance of distinct pauses. At 5 and 8 milligrams per kilogram, *l*-amphetamine produced a regular slowed rate. At 12.5 milligrams per kilogram the lever pressing was suppressed for 193 minutes, and then

resumed at a slightly slowed, even rate with short distinguishable pauses following reinforcement.

At doses of 1 and 2 milligrams per kilogram of *d*-methamphetamine, the over-all running rate of Rat 86 was slowed. Short pauses following reinforcement appeared regularly, in addition to other slightly longer pauses which appeared similar to those seen with the saline and satiation curves. At 3.2 milligrams per kilogram, the rat worked erratically for four reinforcements and then paused for 48 minutes. After this period of no responding, lever pressing resumed at an almost normal rate. Toward the end of the run, distinct pausing again appeared, without changes in the running rate.

Figure 2. Segments taken from cumulative records for Rat 82. Parts A and A' show an atypical approach to satiation. Part B shows a detail of irregular slowing of response rate after administration of 1 milligram per kilogram of *d*-amphetamine.

Rat 88 (Fig. 6) normally produced a stable response rate of about 2.60 responses per second. With approaching satiation, the rate slowed very slightly, with increasingly longer pauses. The last several pauses showed occasional short bursts of from 4 to 10 lever presses per burst. Under the influence of the drugs at the doses used, the rate of responding became regularly slowed, with very few discernible pauses. Occasionally at the higher doses, especially with 12.5 milligrams per kilogram of *l*-amphetamine, the rate immediately following reinforcement was somewhat higher than it was toward the end of the ratio run. This effect showed up as negatively accelerated rate segments between reinforcements.

Rat 182 (Fig. 7) produced a normal lever-pressing rate of about 3.40 responses per second. As the animal became satiated the rate appeared to be unaffected; however, as the pauses became longer, short bursts of 5–10 responses appeared. The drugs induced marked irregularities in the response rate. In some instances at the low doses of these drugs the rate was initially slightly accelerated and then became slowed toward the end of the session. The higher doses showed random mixing of both slowed and increased rates. At 3.2 milligrams per kilogram of *d*-amphetamine the rat frequently continued responding during the 8-second interval that the dipper was available for reinforcement (indicated by the arrows in Fig. 7).

RAT 84
FR-30 MILK

RAT 86
FR-30 MILK

Figure 4. Cumulative records for Rat 86 under conditions noted.

Figure 5. Segments taken from cumulative records for Rat 86. Part A shows the approach of satiation. Part B shows a detail of irregular slowing response rate after 2 milligrams per kilogram of *d*-amphetamine.

somewhat irregular resumption of lever pressing. After 1 milligram per kilogram, at about the midpoint of the session, the rate again appeared to be about normal, although brief pauses occurred after reinforcement. At 2 milligrams per kilogram, after 9 reinforcements, responding completely stopped for 116 minutes. At 3.2 milligrams per kilogram, responding stopped for 137 minutes after 3 reinforcements. With *l*-amphetamine at 5 milligrams per kilogram, the rate after drug administration appeared almost normal; but after about 6 reinforcements, pausing became quite marked and lengthened progressively. At the 26th reinforcement the running rate returned almost to normal. The cumulative curve at 8 milli-

Figure 6. Cumulative records for Rat 88 under conditions noted.

grams per kilogram appeared much the same as the curve for 2 milligrams per kilogram of *d*-amphetamine. A dose of 16 milligrams per kilogram completely suppressed responding for 270 minutes following drug administration; at this point responding resumed at almost the normal rate.

Rat 184 (Fig. 9), with a high normal rate of 3.50 responses per second, initially showed little or no pausing. As satiation approached, the pausing became frequent and quite pronounced. In several of these pauses, occasional short bursts of lever pressing were apparent. The *dl*- and *d*-amphetamine doses created little effect on the response rate. Their main

Figure 7. Cumulative records for Rat 182 under conditions noted.

effect appeared to be that of inducing complete suppression of pressing after drug administration at the higher doses. At all three doses, *l*-amphetamine induced a somewhat irregular decline in the rate; and at doses of 8 and 12.5 milligrams per kilogram, no responding occurred for 2.5 and 103 minutes before the return of lever-pressing behavior.

Rat 186 (Fig. 10), with a normal rate of 2.9 responses per second, showed the approach of satiation by frequent very short pauses with an occasional long one, with little or no change in rate. At the doses used, the amphetamine drugs produced a pronounced slowing of the rate, with frequent pausing both after reinforcement and between reinforcements. Some extremely long pauses were seen at various points during the drug sessions, especially with *d*-amphetamine at 2 milligrams per kilogram and *l*-amphetamine at 5 and 12.5 milligrams per kilogram. With *dl*-amphetamine at 2 and 3.2 milligrams per kilogram, *d*-amphetamine at 2 milligrams per kilogram, and *l*-amphetamine at 8 milligrams per kilogram, responding completely stopped before the ends of the sessions. At 3.2 milligrams per kilogram, *d*-amphetamine caused complete suppression of responding for 147 minutes following drug administration.

Table 1 summarizes the relationship of drug and dosage to the various effects on behavior. Table 2A gives a more detailed summarization of the influence of *dl*-, *d*-, and *l*-amphetamine on the individual rats. The alteration of response rate is expressed as the ratio of the rate with drug to the normal rate. The time spent pausing, expressed in minutes, includes all pauses of 5 seconds or greater and the time spent not responding immediately following the return to the box after drug administration. The number of pauses includes only those pauses of 5 seconds or more. Table 2B presents the means of 10 nondrug sessions for each rat showing normal response rates, times spent pausing, and numbers of pauses. Saline control data are also shown in this Table.

DISCUSSION

As the cumulative curves indicate, the amphetamine compounds and *d*-methamphetamine influenced the FR 30 performance in three ways: *a*) the response rate was altered; *b*) the

Figure 8. Cumulative records for Rat 183 under conditions noted.

RAT 184
FR-30 MILK

dl-AMPHETAMINE

d-AMPHETAMINE

l-AMPHETAMINE

Figure 9. Cumulative records for Rat 184 under conditions noted.

frequency and duration of pausing increased (straining); *c*) the rats failed to resume pressing the lever when returned to the box after the 20- or 30-minute waiting period which immediately followed drug administration.

In general, the effects of the drugs in each rat were manifested by combinations of at least two of these three alterations of the lever-pressing behavior. In some rats, e.g., Rats 84, 183, and 184, there was predominantly little alteration in response rate but there were

marked changes in the number of pauses following reinforcement. Other animals, Rats 82 and 88, for the most part, showed a slowing of rate with a minimum of pausing. Rats 86, 182, and 186 produced curves which showed both a slowing of rate and the appearance of definite pausing. The delayed resumption of responding occurred at least once in all the rats except 88. In Rat 182, this effect was seen only at the high dose of *d*-amphetamine. At the other extreme, Rat 84 exhibited this in all instances except at the low doses of *dl*- and *d*-amphetamine and *d*-methamphetamine. Rat 183 showed this delay only at 16 milligrams per kilogram of *l*-amphetamine; however, with the two high doses of *d*-amphetamine and the dose of 8 milligrams per kilogram of *l*-amphetamine after 3–8 reinforcements, extremely long pauses of 100 minutes or more occurred.

In spite of the variability of effects among animals, the general types of drug effects varied little from one compound to another in the individual rats. The chief variant appeared to be an enhancement of the particular type of influence of the drug. However, the actions of one compound in a rat did not always present a typical dose-response sequence, e.g., Rats 88 and 186. (See Table 2A for these and other examples.)

The *dl*- and *d*-amphetamine and *d*-methamphetamine were all given at the same doses: 1, 2, and 3.2 milligrams per kilogram. Considering the three general effects of these drugs, the cumulative curves indicated that *d*-amphetamine was the most potent of these three compounds. In two of the three rats, *d*-methamphetamine appeared to be the next most

Figure 10. Cumulative records for Rat 186 under conditions noted.

Table 1
Summary of Effects on Drug-dose Relationships in Individual Rats

Effect	Rat 82			Rat 84			Rat 86		
	<i>a</i>			<i>a</i>			<i>a</i>		
	LMH	LMH	LMH	LMH	LMH	LMH	LMH	LMH	LMH
Dose									
dl-amphetamine	0	+	+	-	+	+	0	+	+
d-amphetamine	+	+	+	-	+	+	+	+	+
l-amphetamine	+	+	+	-	+	+	+	+	+
d-methamphetamine	+	+	+	0	0	+	+	+	+
satiation	+	-	+	+	+	+	0	+	+

Effect	Rat 88			Rat 182			Rat 183		
	<i>a</i>			<i>a</i>			<i>a</i>		
	LMH	LMH	LMH	LMH	LMH	LMH	LMH	LMH	LMH
Dose									
dl-amphetamine	+	+	0	-	+	+	0	0	-
d-amphetamine	+	+	0	-	+	+	0	0	-
l-amphetamine	+	+	0	-	+	+	-	-	-
satiation	0	-	-	0	+	+	-	-	-

Effect	Rat 184			Rat 186		
	<i>a</i>			<i>a</i>		
	LMH	LMH	LMH	LMH	LMH	LMH
Dose						
dl-amphetamine	-	-	-	+	+	+
d-amphetamine	-	-	-	+	+	+
l-amphetamine	+	+	+	+	+	+
satiation	0	+	+	-	-	-

Key: L M H low, medium, high doses Effect: *a* alteration of response rate
b pausing after reinforcement
c long pause following drug administration

+ change from normal
- no change from normal
0 mixed or questionable change

Table 2A
Effects of *dl*, *d*, and *l*-Amphetamine on Rate of Responding (Ratio of Rate with Drug to Normal Rate), Total Time Spent Pausing, and Number of Pauses

Rat No.	<i>dl</i> -Amphetamine				<i>d</i> -Amphetamine				<i>l</i> -Amphetamine			
	Dose (mg/kg)	Rate Ratio	Time (min)	No. of Pauses	Dose (mg/kg)	Rate Ratio	Time (min)	No. of Pauses	Dose (mg/kg)	Rate Ratio	Time (min)	No. of Pauses
82	1	0.92	0.88	7	1	0.66	2.30	24	5	0.48	1.12	31
	2	0.44	0.99	17	2	0.64	129.16	48	8	0.56	137.90	16
	3.2	0.44	12.96	106	3.2	0.62	213.70	55	16	0.40	156.71	73
84	1	0.93	0.18	3	1	0.88	16.17	34	5	0.93	124.00	32
	2	0.73	45.08	25	2	1.19	130.20	41	8	0.92	62.20	37
	3.2	0.76	139.36	24	3.2	1.14	87.11	26	16	0.87	235.00	34
86	1	0.86	9.00	39	1	0.35	10.20	28	5	0.27	16.79	57
	2	0.44	30.06	82	2	0.37	127.50	65	8	0.23	36.00 ^a	53
	3.2	0.38	102.00	68	3.2	0.72	220.40	21	12.5	0.87	233.20	83
88	1	0.43	5.53	38	1	0.40	1.26	15	5	0.39	1.60	15
	2	0.73	1.41	5	2	0.20	5.24	98	8	0.26	0.63	33
	3.2	0.23	2.24	50	3.2	0.45	1.19	13	12.5	0.25	4.00	58
182	1	0.73	0.08	1	1	0.67	0.06	1	5	0.99	2.05	38
	2	0.53	1.36	10	2	0.43	14.50	18	8	0.76	2.48	26
	3.2	0.42	19.00 ^b	22	3.2	0.64	211.80	42	12.5	0.45	11.00 ^d	—
183	1	0.67	1.17	22	1	0.80	7.67	47	5	1.06	46.87	55
	2	0.59	9.04	54	2	0.65	122.07	17	8	0.82	109.28	40
	3.2	0.68	13.00 ^c	21	3.2	0.83	150.63	50	16	0.48	247.40	20
184	1	0.76	0.30	5	1	0.66	0.10	1	5	0.72	3.46	38
	2	0.73	55.00	2	2	0.71	1.34	3	8	0.55	4.55	38
	3.2	0.84	97.00	1	3.2	0.91	213.00	0	12.5	0.33	106.10	25
186	1	0.33	17.14	93	1	0.43	13.74	56	5	0.50	64.34	84
	2	0.22	55.86	72	2	0.50	148.00	58	8	0.27	31.00 ^h	87
	3.2	0.29	34.64 ^e	92	3.2	0.46	151.00	63	12.5	0.50	204.80	81

^a23 reinforcements^e22 reinforcements^b18 reinforcements^f12 reinforcements^c20 reinforcements^g29 reinforcements^d11 reinforcements^h25 reinforcements

Table 2B
Normal and Saline Control Data for Table 2A

Rat No.	Normal Means			Saline		
	Rate (response per sec)	Time (minutes)	No. of Pauses	Rate Ratio	Time (minutes)	No. of Pauses
82	2.50	0.63	14.1	0.99	0.49	6
84	2.55	0.86	20.0	0.99	0.46	19
86	3.22	1.68	6.4	1.00	1.57	6
88	2.60	1.20	3.5	1.00	0.87	6
182	3.40	1.19	31.3	0.94	1.13	14
183	3.13	1.16	24.3	0.98	0.84	26
184	3.47	0.15	2.0	1.10	0.02	1
186	2.91	4.06	35.8	1.09	---	18

active compound. Except for Rats 86 and 186, *dl*-amphetamine appeared next in the order of potency. In Rat 186 the *dl*- compound was more potent than its *d*- isomer. Rat 86 showed greater effect with *dl*-amphetamine than with *d*-methamphetamine. Also, *l*-amphetamine, which was given in a higher range of doses, presented the same general picture as the other drugs in their lower range.

With the notable exception of Rat 82, these rats showed satiation curves typical of those described by Sidman and Stebbins (1954); i.e., as satiation approached, the response rate was maintained, but the pauses after reinforcement became more frequent and of greater length. Toward the completion of the satiation sessions, Rats 86, 88, 182, and 184 began to show short bursts of lever pressing between reinforcements. These appeared as "knees," in both nominal pausing and, occasionally, in the middle of protracted pauses of several minutes or more. With a few rare exceptions, these bursts appeared to occur at the individual rat's normal rate. Rat 82, whose satiation curve became very irregular toward the end of the session, showed a variety of intermittent bursts of lever pressing. Some of these appeared almost normal, while other small segments were quite definitely slowed. In many respects, segments of this rat's satiation curve were similar to the effects of the drugs both in declination and irregularity of responding rate. Rats 84, 86, and 183 also showed similarities in their approach to satiation and the effects of these drugs on this FR schedule. Rats 186 and 88 differed from the other rats inasmuch as in approaching satiation the rates remained normal or almost normal; but with drugs the running rates were clearly depressed and/or irregular.

In some respects, the slowed irregular segments that occurred in some of the rats' drug curves appeared as aberrant forms of ratio straining in which very brief bursts of lever pressing were followed by extremely short (on the order of 2-5 seconds) pauses (Fig. 2 and 5), which are not normally seen in sessions without drugs. This type of alteration of the response curves appeared similar to the "responses at a lower rate" seen between the long pause and high rate just before reinforcement described by Morse and Herrnstein (1956). They also noted an increase in occurrence of the "low and intermediate rates" with methamphetamine.

The effects of slowed and/or irregular response rates and of the increased frequency and duration of pausing in rats with these sympathomimetic amines could be described in terms of "a lowering of the threshold for fixed-ratio straining." However, in respect to the pausing alone, these drugs appeared to have an influence that mimics, in exaggerated form, the effects of a high number of accumulated reinforcements.

The delay in the return of responding appeared as the peak effect of the drug in those instances in which it occurred. Likewise, extremely long pauses in the middle of a session or the complete cessation of lever pressing before the maximum number of reinforcements were obtained appeared as manifestations of peak effects.

SUMMARY

Eight rats, trained on an FR 30 schedule for milk reinforcement, were given *dl*-, *d*-, and *l*-amphetamine and *d*-methamphetamine in appropriate dose ranges. The resulting cumulative curves were examined for alteration of the FR behavior.

In this study the drugs influenced the performance in three broad ways: *a*) the response rate was altered, generally slowed either smoothly or irregularly; *b*) the frequency and duration of pausing following reinforcement increased; *c*) the rat temporarily failed to resume responding when returned to the cage after drug administration.

The effects of the drugs varied among animals. However, in the individual rats the general types of effects varied little among drugs.

A discussion of the results is presented, comparing normal (control) FR curves and satiation curves with the general types of behavioral effects obtained with the drugs.

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