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EFFECTS OF *d*-AMPHETAMINE, MONOMETHOXY-AMPHETAMINES AND HALLUCINOGENS ON SCHEDULE-CONTROLLED BEHAVIOR[1]

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ABSTRACT

HARRIS, R. ADRON, DIANE SNELL AND HORACE H. LOH: Effects of *d*-amphetamine, monomethoxyamphetamines and hallucinogens on schedule-controlled behavior. J. Pharmacol. Exp. Ther. 204: 103-117, 1978.

The effects of 16 drugs were studied in rats responding under fixed-ratio (FR 30) and fixed-interval (FI 2 minute) schedules of food presentation. The drugs tested included lysergic acid diethylamide (LSD), dimethyltryptamine, mescaline, *d*-amphetamine and 12 methoxylated amphetamines. All of the drugs decreased the average rates of responding under both schedules, but their potencies varied widely. For example, with LSD, the most potent drug tested, doses of 0.1 to 0.3 mg/kg were sufficient to reduce responding while with dimethyltryptamine and mescaline, doses of 10 to 30 mg/kg were required to clearly reduce responding. For the 12 drugs which are known to produce hallucinogenic effects, their potencies in reducing responding were positively correlated with their reported potencies in producing these subjective effects in humans. Although all of the drugs decreased the average rates of responding, alterations in the patterns of responding under the FR and FI schedules varied among the drugs. Analysis of responding under the FI schedule indicated that *d*-amphetamine, *m*-methoxyamphetamine, *p*-methoxyamphetamine, LSD and 3,4-methylenedioxyamphetamine generally increased the low rates of responding occurring at the beginning of each interval and decreased the high rates of responding occurring later in each interval (rate-dependent effects). The other drugs generally decreased responding throughout the interval. These results are discussed in terms of the known neurochemical effects of these drugs.

A variety of hallucinogenic drugs have been tested in humans and the subjective effects as well as the relative potencies of these agents have been reported (Shulgin *et al.*, 1969; Shulgin, 1973a). In nonhuman subjects, comparisons of the behavioral effects of a number of hallucinogens within a single study have been more limited. Smythies *et al.* (1967) determined the relative potencies of several methoxylated amphetamines in disrupting performance maintained by a shock avoidance schedule but presented little data concerning the doses used and no quantification of the effects of the drugs on responding. Quantitative comparisons of the behavioral effects of several hallucinogens have been reported using underwater maze perfor-

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mance in rats (Uyeno, 1968; Uyeno and Mitoma, 1969) and size discrimination in monkeys (Uyeno *et al.*, 1968). As many studies of the effects of hallucinogens on schedule-controlled behavior have involved only lysergic acid diethylamide (LSD) or mescaline (Smythies and Sykes, 1964; Appel, 1971; Tilson and Sparber, 1973; Dykstra and Appel, 1972; Altman and Appel, 1975), the present investigation was undertaken to compare the effects of a number of hallucinogens on behavior maintained by fixed-interval (FI) and fixed-ratio (FR) schedules of food presentation.

In addition, the behavioral effects of *d*-amphetamine and monomethoxyamphetamines are of interest as introduction of a single methoxy group on the aromatic ring of amphetamine results in compounds with behavioral and biochemical effects which are substantially different from those of the parent compounds. In particular, *p*-methoxyamphetamine (PMA) has been shown to be a potent hallucinogen in humans (Shulgin *et al.*, 1969). PMA, in contrast to *d*-amphetamine, does not produce stereotyped behavior in rodents (Tseng and Loh, 1974) and increases locomotor activity only if large doses (30 mg/kg) are administered (Hitzemann *et al.*, 1971; Tseng and Loh, 1974). Biochemical studies (Hitzemann *et al.*, 1971; Tseng *et al.*, 1974, 1976) have indicated that PMA has more pronounced effects on the uptake and release of brain serotonin (5-HT) and less effect on the uptake and release of brain dopamine than does *d*-amphetamine. In addition, *m*-methoxyamphetamine (MMA) is less effective than PMA in altering brain 5-HT function but is more effective than PMA in affecting brain dopamine function, while *o*-methoxyamphetamine (OMA) has little effect on 5-HT, dopamine or NE uptake or release except at very high concentrations (Tseng *et al.*, 1976). Due to these biochemical differences among these four compounds, it was of interest to compare their effects on schedule-controlled behavior. Although the effects of amphetamine on behavior under schedules of food presentation have been well studied, the monomethoxyamphetamines apparently have only been evaluated using shock-avoidance behavior (Smythies *et al.*, 1967).

The effects of drugs on responding under FI schedules are of particular interest, as it has been shown that *d*-amphetamine as well as a variety of other drugs increase the normally low rates of responding occurring at the beginning of the interval but decrease the normally high rates of responding occurring at the end of the interval (Dews, 1958; McMillan, 1969; Sanger and Blackman, 1976). Because these effects can be described as a function of the control rate of responding (Dews, 1964), they are generally termed "rate-dependent." Regarding hallucinogens, several experiments suggest that LSD (Altman and Appel, 1975), mescaline (Tilson and Sparber, 1973) and 2,5-dimethoxy-4-methylamphetamine (DOM) (Tilson *et al.*, 1975a; Harris *et al.*, 1977b) may have rate-dependent effects. The present study extends these observations by comparing the effects of 16 hallucinogenic and nonhallucinogenic amphetamine and tryptamine derivatives on behavior maintained by a FI 2-minute schedule of food presentation.

Methods

Animals. Fifteen male Sprague Dawley rats obtained from Simonsen Laboratories, Gilroy, Calif. and weighing between 400 and 500 g when given free access to food and water were used. They were deprived of food and maintained at 80% of their free-feeding weights during these experiments. These animals had no previous experimental history.

Apparatus. Standard rat test cages (Grason-Stadler, West Concord, Mass.) 23 cm long, 29 cm wide and 19 cm high were installed in sound attenuating chambers (Grason-Stadler). The manipulandum consisted of a cylindrical lever 0.6 cm in diameter and 2.5 cm long (BRS/LVE, Beltsville, Md.) equipped with microswitches such that movement of the lever (about 30 *g* force required at the tip) in a vertical or lateral direction would be recorded as a response. The lever protruded from the wall containing the food bin and was placed 9 cm above the cage floor and 9 cm from the cage wall. Conventional relay programming and recording equipment located in an adjacent room controlled the delivery of food and recorded the pattern of responding.

Procedure. Six animals were trained under a fixed-ratio 30 (FR 30) schedule and nine were trained under a fixed-interval 2-minute (FI 2) schedule (Ferster and Skinner, 1957) of food presentation. Under the FR 30 schedule, the 30th response produced two 45 mg food pellets (P. J. Noyes Co., Lancaster, N.H.), whereas under the FI 2 schedule, the first response after 2 minutes had elapsed produced two 45 mg food pellets. The cumulative responses within each 20-second segment of the fixed interval were recorded by digital counters. The sessions under the FI 2 schedule were terminated after presentation of 24 fixed intervals or 50 min-

utes, whichever occurred first. Sessions under the FR schedule were terminated after 30 minutes. Sessions were conducted 5 days each week. After about 8 weeks of performance under the FI 2 and FR 30 schedules, responding was judged to be stable by inspection of the cumulative records and calculated response rates, and drug injections were begun.

Drugs. Drugs and their suppliers were: lysergic acid diethylamide tartrate (LSD) and 3,4-methylenedioxyamphetamine oxalate (MDA) (courtesy of the National Institute of Mental Health); mescaline sulfate, dimethyltryptamine base (DMT), and *d*-amphetamine sulfate (Sigma Chemical Company, St. Louis, Mo.); *d*-*p*-methoxyamphetamine hydrochloride (PMA) (courtesy of Dr. Charles Barfnecht, College of Pharmacy, University of Iowa, Iowa City, Iowa); *dl*-*m*-methoxyamphetamine oxalate (MMA) and *dl*-*o*-methoxyamphetamine oxalate (OMA), 2,4-dimethoxyphenylisopropylamine hydrochloride (2,4-DMA), 2,5-DMA hydrochloride, 3,4-DMA hydrochloride, 2,4,6-trimethoxyphenylisopropylamine hydrochloride (2,4,6-TMA), 2,4,5-TMA oxalate (Fox Chemical Co., Tucson, Ariz.). Initial studies indicated an onset of action of less than 10 minutes for all drugs except MMA, which did not alter responding until about 30 minutes after injection. Thus, drugs were injected 5 minutes before the beginning of each session, except for MMA which was injected 30 minutes before the session. In other preliminary studies, LSD, *d*-amphetamine and PMA were found to produce comparable results when injected either s.c. or i.p., while mescaline was found to be more potent when injected i.p. than when injected s.c. LSD, *d*-amphetamine, PMA, OMA, MMA and DMT were given s.c., while all other drugs were given i.p. All drugs were dissolved in 0.9% NaCl and an injection volume of 1 ml/kg was used. Dosages in milligrams per kilogram are based on the salts of the compounds, except for DMT, for which the base was used. Dosages in micromoles per kilogram are calculated for the bases. Each dose of each drug was administered once to three animals performing under the FR schedule (except for MDA and 2,3,6-TMA which were given to six animals performing under the FR schedule), and twice to three animals performing under the FI schedule. Drug injections were separated by at least 72 hours. The drugs were administered to the various groups of animals in the following order: FR group I (nos. 1, 2, and 4), *d*-amphetamine, PMA, MMA, OMA, mescaline, 2,5-DMA, 3,4-DMA, 2,4,5-TMA, 2,3,5-TMA, 2,3,6-TMA and MDA; FR group II (nos. 13, 14 and 15), DMT, LSD, 2,4-DMA, 2,3,4-TMA, 2,4,6-TMA, 2,3,6-TMA and MDA; FI group I (nos. 3, 5, and 6), *d*-amphetamine, PMA, LSD, 2,4,5-TMA, 2,3,5-TMA and 2,3,6-TMA; FI group II (nos. 7, 8, and 10), OMA, MMA, DMT, mescaline and MDA; FI group III (nos. 9, 11, and 12), 2,4-DMA, 2,5-DMA, 3,4-DMA, 2,3,4-TMA and 2,4,6-TMA.

Measurement of drug effects. The average control response rates were determined individually for each drug using 4 to 6 saline injection days or noninjection days occurring before and 4 to 6 saline injection days or noninjection days occurring after determination of the dose-response curve of each drug. In addition, 1 or 2 noninjection days occurring during each drug series were used for control values. Saline injections did not alter responding, and the data from saline injection days and noninjection days were averaged together. The rates within successive sixths of the FI 2 (local rates) were determined and plotted as a function of the local control rates as done by Dews (1964) and others (Kelleher and Morse, 1968; Leander and McMillan, 1974). The data for each animal were fitted to a line by the method of least squares and the slope, 95% confidence limits of the slope, *y*-intercept and correlation coefficient were calculated (Goldstein, 1964). The data are presented as the mean derived from the three animals in each experiment.

Results

Effects of *d*-amphetamine, *d*-PMA, *dl*-MMA and *dl*-OMA on average measures of responding under FR and FI schedules. All four of these drugs reduced the average response rates for animals performing under FR 30 or FI 2-minute schedules (fig. 1). However, the potency of these compounds in decreasing response rates differed markedly. Under the FI schedule of food presentation, *d*-amphetamine was somewhat more potent than PMA in decreasing rates of responding and about 15 times more potent than MMA as judged by estimating the dose of each drug required to reduce responding to 50% of control levels. Under the FR schedule, PMA was slightly more potent than *d*-amphetamine, while MMA was about 9 times less active than *d*-amphetamine. OMA was less potent than MMA, inasmuch as even the highest dose of OMA tested (30 mg/kg) was not sufficient to decrease responding by 50% under either the FR or FI schedule.

An examination of the cumulative records of responding under the FR schedule indicated that all four drugs decreased response rates by producing short, irregular pauses throughout the ratio. This disruption of performance by these drugs was similar to the effects of *d*-amphetamine on responding under FR schedules reported by Owen (1960).

Effects of *d*-amphetamine, *d*-PMA, *dl*-MMA and *dl*-OMA on local rates of responding under the FI 2 schedule. In order to analyze drug effects on local response rates, the re-

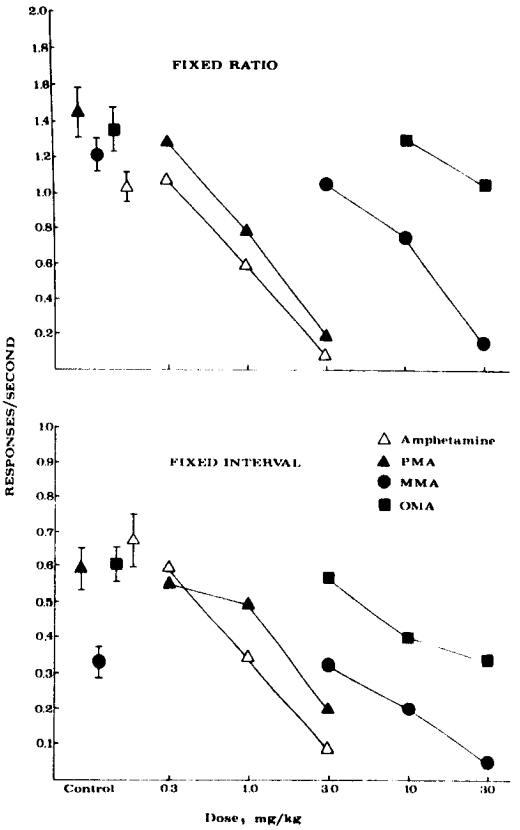

FIG. 1. Effects of *d*-amphetamine, *d*-PMA, *dl*-MMA and *dl*-OMA on average rates of responding under FR 30 and FI 2 schedules. Control values are means from 8 to 12 sessions for three rats; vertical bars represent ± 3 S.E. Each point represents duplicate (FI) or single (FR) determinations in three rats.

sponse rate during each (6) 20-second segment of the FI was calculated. The effects of selected doses of each drug on these local response rates are shown as a function of the local control rate in figures 2 and 3.

Figure 2 shows that *d*-amphetamine (0.3 and 1.0 mg/kg) greatly increased the rate of responding when the local control rate was low (less than 0.5 response/sec) while decreasing the rates of responding when the control rate was higher (greater than 0.5 response/sec). In comparison, PMA in doses of 1 or 3 mg/kg decreased the rates of responding during most segments of the interval but generally increased responding occurring at the lowest control rates. Thus, *d*-amphetamine and PMA both produced rate-dependent effects. From figure 3 it can be seen that MMA (10 and 30 mg/kg) generally increased the rates of responding when the control rate was low or intermediate, while decreasing the rates of responding associated with the highest control rates. These rate-dependent effects are similar to those seen with *d*-amphetamine and PMA except that with MMA the rate of responding during the first segment of each interval (filled symbols in fig. 3) was not increased as much as were the rates of responding during the second or third segments. This effect was not seen with *d*-amphetamine and was seen with only one animal with *d*-PMA (filled circles, fig. 2). OMA produced moderate decreases in most rates of responding and produced none of the increases in rates of responding seen with amphetamine, PMA and MMA.

The rate-dependent effects of these four drugs can be summarized and compared on the basis of the slopes and intercepts of regression lines fitted to data such as those in figures 2 and 3 (table 1). If the slope of the regression line is taken as a measure of rate dependence (*i.e.*, the steeper the slope, the more pronounced the rate-dependent effects of the drug), then the data in table 1 indicate that the two lower doses of PMA did not produce the marked rate dependence seen with the same doses of *d*-amphetamine. However, all three doses of MMA produced a similar degree of rate dependence as did the three doses of *d*-amphetamine tested. The highest dose of PMA tested (3 mg/kg) produced a degree of rate dependence which was not significantly different (as judged from the confidence limits of the slopes in table 1) from that found with the highest doses of *d*-amphetamine.

Effects of hallucinogens on responding under a FR schedule. All of the hallucinogens tested decreased the average rate of responding maintained under the FR 30 schedule, but individual drugs varied greatly in their potency. Figure 4 (upper panel) shows the effects of five drugs, which are representative of the 12 tested. It can be seen that LSD was about 30 times more potent in reducing responding than the next most active drug, 2,4,5-TMA. MDA and PMA were also quite active, being about equipotent with 2,4,5-TMA. The least potent drug for disrupting performance under the FR schedule was mescaline, requiring a dose of 30 mg/kg to reduce responding by about 50%. The drug effects are presented in figure 4 as a

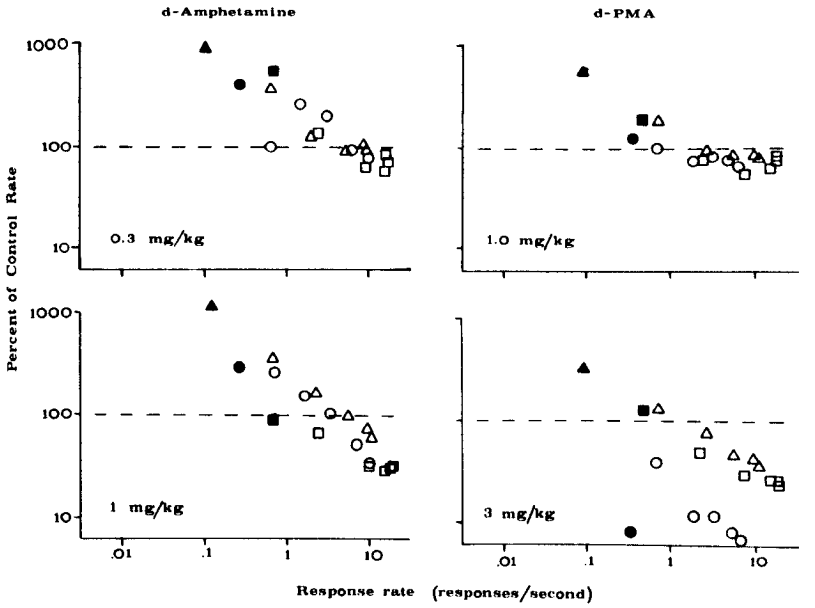

FIG. 2. Effects of 0.3 and 1.0 mg/kg of *d*-amphetamine and 1.0 and 3.0 mg/kg of *d*-PMA on rates of responding during each 20-second segment of the FI 2 minute schedule. Abscissa: control rate of responding for each 20-second segment, log scale. Ordinate: rate of responding after drug injection expressed as a percentage of the control rate, log scale. The dashed lines at 100% of the control rate indicate no change from the control data. Circles, triangles and squares represent data from three different rats. Each point is the mean of duplicate determinations. The average slopes, *y*-intercepts when $x = 1$ response/sec for regression lines fitted to these points are given in table 1. Filled symbols represent values from the first 20-second segment of each interval (*i.e.*, the segment immediately following food presentation).

percentage of control responding. It should be noted that for the six animals performing under the FR schedule the control rate was about 1.8 responses/sec. A more complete comparison of the potencies of the drugs tested is presented in figure 9 and discussed below. Although all of the drugs decreased the overall rates of responding under the FR schedule, their effects on the pattern of responding could be used to divide them into two groups: with the exception of 2,3,6-TMA, those which were given to animals nos. 13, 14 and 15 produced periods of no responding alternating with periods of normal responding (fig. 5, top panel) and those which were given to animals nos. 1, 2 and 4 produced slower and somewhat erratic rates of responding throughout the session (fig. 5, bottom panel). Only two drugs, MDA and 2,3,6-TMA were given to both groups of rats. In the case of the drugs given to the first group of animals, the periods of no responding appear to be due to a lengthening of the normally brief (3-6 second) postreinforcement pause to a pause lasting from 30 seconds to 15 minutes. Although the cumulative records in figure 5 only show the effects of each drug in one rat, similar results were obtained with all three rats in each group. However, the differences in drug effects also may be related to individual differences between animals as MDA produced pauses in responding in animals nos. 13, 14 and 15 while producing slow responding in animals nos. 1, 2 and 4 (fig. 5). In contrast, 2,3,6-TMA produced both slow responding and pausing in both groups of animals (fig. 5).

Effects of hallucinogens on average rates of responding under a FI schedule. All of the hallucinogens tested reduced the average rates of responding under the FI 2-minute schedule (fig. 4, lower panel). As was seen with responding under the FR schedule, the potency of the drugs in reducing responding varied widely with LSD, the most potent drug, being about 100 times more active than mescaline, one of the least potent drugs tested. The most active trimethoxyamphetamine (TMA) was 2,4,5-TMA, which had about the same potency as 3,4-MDA and PMA. All three dimethoxyamphetamines (DMA) tested (2,4-DMA, 2,5-DMA and 3,4-DMA) were of about equal potency,

being only slightly more active than mescaline. The data in figure 4 are presented as a percentage of control responding to facilitate comparisons of the effects of the various drugs, but it should be noted that the average control rate of responding for the nine animals performing under the FI schedule was about 0.6 response/sec.

Comparison of the potencies of hallucinogens in reducing responding under FI and FR schedules. The potency of each drug was estimated by determining the dose required to reduce the average FI and FR response rates to 50% of the control rate of responding using data such as those shown in figure 4. The response rate (as a percent of control responding) was plotted *vs.* the log of the dose of the drug and a straight line was fitted to the points by least squares regression analysis. The dose at which response rate was equal to 50% of control was calculated from this line. These doses were determined for each drug and were termed "FI ED50" and "FR ED50" and expressed as micromoles per kilogram (calculations based on the molecular weight of the base) to correct for differences in formula weights between the different compounds. These FI ED50 and FR ED50 values, respectively, for the various drugs were: LSD 0.50, 0.27; *d*-amphetamine 5.1, 8.8; MDA 9.7, 9.0; PMA 11, 5.6; 2,4,5-TMA 12, 11; 2,4,6-TMA 21, 20; 2,4-DMA 31, 16; 2,5-DMA 40, 41; 3,4-DMA 42, 58; 2,3,4-TMA 58, 50; 2,3,5-TMA 67, 63; 2,3,6-TMA 67, 66; DMT 28, 78; mescaline 50, 90; MMA 78, 78; OMA > 120, > 120.

Effects of hallucinogens on local rates of responding under a FI schedule. The effect of these drugs on the local rates of responding during the FI schedule were evaluated as described above for *d*-amphetamine and the monomethoxyamphetamines. These data are displayed in figures 6, 7 and 8 and in table 2.

The effects of DMT and LSD on local rates of responding are shown in figure 6. DMT decreased responding irrespective of the control rate of responding (all points, except one, fall below the dotted line, which represents 100% of control), while LSD generally increased re-

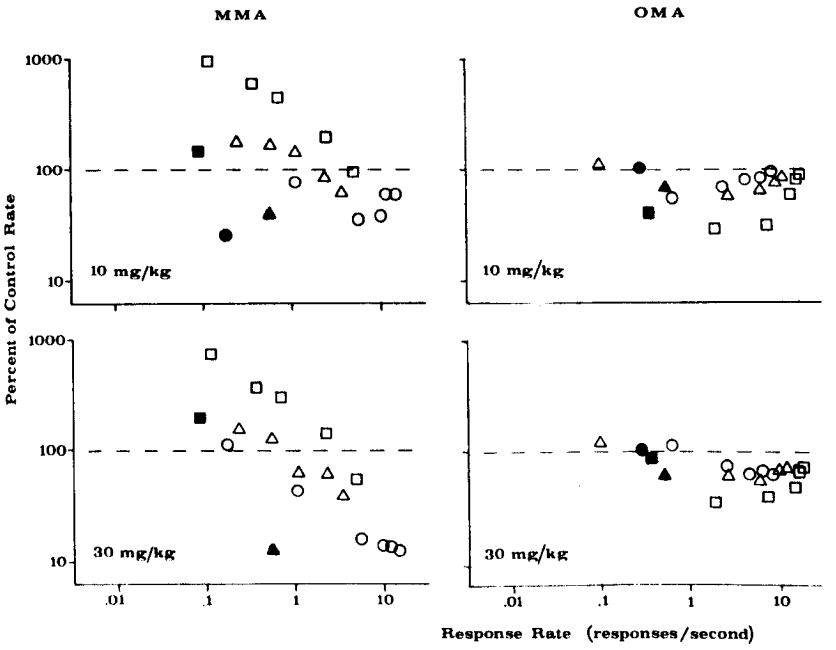

FIG. 3. Effects of 10 and 30 mg/kg of MMA and OMA on rates of responding during each 20-second segment of the FI 2-minute schedule. Abscissa: control rate of responding for each 20-second segment, log scale. Ordinate: rate of responding after injection expressed as a percentage of the control rate, log scale. The dashed lines at 100% of the control rate indicate no change from the control data. Circles, triangles and squares represent data from three different rats. The average slopes, *y*-intercepts when $x = 1$ response/sec and correlation coefficients for regression lines fitted to these points are given in table 1. Filled symbols represent values from the first 20-second segment of each interval (*i.e.*, the segment immediately following food presentation.

TABLE 1

Drug effects evaluated as a function of the control rate of responding

Shown here are the average slopes and correlation coefficients (r) of the regression lines and average response rates after drug injection as a percentage of control when the control rate is 1 response/sec. Portions of these data are derived from figures 3 and 4. Data are means derived from duplicate determinations in three animals. Ninety-five percent confidence limits are given in parentheses.

Drug	Dose	Slope	y-Intercept as % of x when x = 1 response/sec	Correlation Coefficient
	mg/kg	*degrees*		
d-amphetamine	0.3	−26 (−34 to −15)	86 (56–117)	0.88
	1.0	−28 (−32 to −24)	47 (26–66)	0.98
	3.0	−27 (−34 to −20)	6 (0–34)	0.88
dl-MMA	3.0	−15 (−22 to −9)	108 (75–140)	0.87
	10.0	−20 (−29 to −10)	55 (23–88)	0.78
	30.0	−29 (−34 to −23)	25 (6–45)	0.98
d-PMA	0.3	−4.1 (−9 to 1)	99 (61–134)	0.61
	1.0	−15 (−20 to −10)	70 (41–102)	0.93
	3.0	−20 (−29 to −9)	22 (0–48)	0.80
dl-OMA	3.0	5.0 (1 to 9)	93 (59–128)	0.60
	10.0	2.6 (−5 to 10)	68 (33–101)	0.42
	30.0	−6.1 (1.2 to −13)	59 (19–97)	0.59

sponding when the control rate was low and decreased responding when the control rate was high. Figure 7 indicates that the effects of mescaline and 2,4,6-TMA were similar to the effects of DMT as these drugs generally decreased rates of responding, although in one animal there were increases for some of the lower rates of responding. Other TMAs also showed large differences between individual animals with each drug generally decreasing responding throughout the interval in most animals while increasing responding in a few animals. However, these increases in responding could not be described as a linear function of the control rate of responding. This is in contrast to the results with *d*-amphetamine, where clear rate-dependent effects were seen in all animals, and these effects could be described as a linear function of the log of the control rate. The effects of 3,4-MDA and the structurally similar 3,4-DMA are compared in figure 8. MDA at a dose of 3 mg/kg produced clear rate-dependent effects as it increased the lowest rates of responding while decreasing higher rates of responding in a linear fashion for all three animals. As is shown in table 2, MDA was the only hallucinogen that produced a slope steeper than −20° and a correlation coefficient greater than 0.9, indicating pronounced rate-dependent effects. The DMA compounds, represented by 3,4-DMA in figure 8, resembled the TMA derivatives in that they generally decreased responding, but some doses increased the lower rates of responding in some animals. The data from these 12 drugs are summarized in table 2 and indicate that only

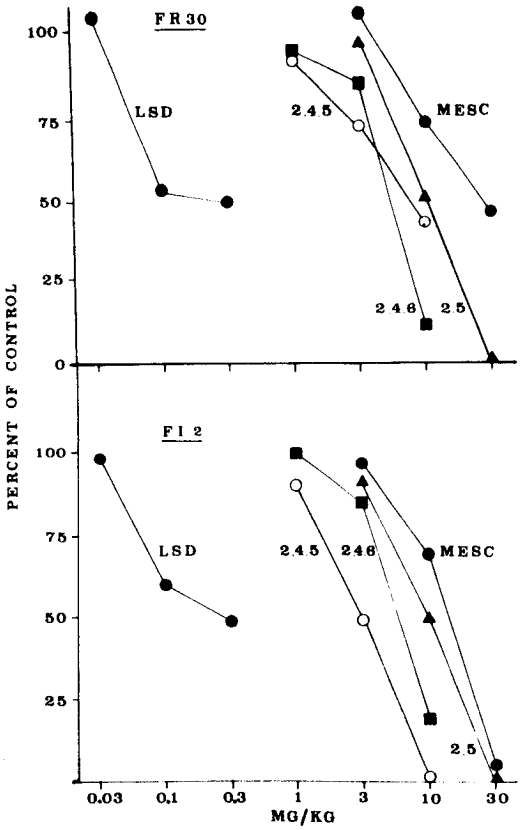

FIG. 4. Effects of LSD, 2,4,5-TMA, 2,4,6-TMA, 2,5-DMA and mescaline on average rates of responding under FR and FI schedules of food presentation. Dosage, as the salt, is given on the abscissa as a log scale, while the ordinate represents a percentage of the control rate of responding. Average control rate of responding for the FR groups was 1.8 responses/sec, while that of the FI groups was 0.6 response/sec. FR data are means of single determinations in three rats, while the FI data are from duplicate determinations in three rats.

MDA and LSD produced clear rate-dependent effects.

Discussion

All of the drugs tested decreased the average rates of FR and FI responding, but their potencies in producing these rate decreases varied considerably. In regard to *d*-amphetamine and the monomethoxyamphetamines, *d*-amphetamine and PMA were the most potent, with MMA being about 10 to 15 times less potent than PMA and OMA being even less active than MMA.

Although *d*-amphetamine only decreased the average overall rates of responding under the FI schedule in these experiments, low doses of the drug have been reported to increase the average rates of FI responding in other studies (Smith, 1964; Tilson and Sparber, 1973; Leander and McMillan, 1974). Our failure to observe these increases in average rates of responding may be due, at least in part, to the use of a relatively short interval (2-minutes) in conjunction with a manipulandum (multidirectional lever), which resulted in much of the FI responding occurring at rather high rates (1 to 2 responses/sec), and high rates of responding often do not show increases in rates of responding after *d*-amphetamine (McMillan, 1969).

In the group of hallucinogens, LSD was clearly the most active in reducing responding; it was 100 times more potent than mescaline in reducing responding under the FI schedule and about 300 times more potent in reducing responding under the FR schedule. Mescaline was the least potent hallucinogen tested. The potencies of several of these drugs in disrupting underwater maze performance by rats (Uyeno, 1968; Uyeno and Mitoma, 1969) and size discrimination performance by squirrel monkeys (Uyeno *et al.*, 1968) have been determined and are generally similar to the values obtained in the present study for the disruption of the schedule-controlled behavior of rats.

It is of interest to compare the clinical potencies of the hallucinogens for producing subjective effects (such as euphoria, anxiety, shimmering of the visual field, intensification of color perception and patterned imagery with undulating shapes) with their potencies for reducing FI and FR responding to 50% of control. When these ED50 values for FI and FR responding are plotted *vs.* the dose (in micromoles of base per kilogram) of each drug reported to be the lowest dose at which any of the subjective effects described above were consistently noted (threshold dose), the points approximate a straight line (fig. 9). The potencies of these drugs in disrupting FI and FR responding in rats are positively correlated with their potencies in producing subjective effects in humans. The compound 2,3,4-TMA (open circles, fig. 9) was reported to be inactive in humans at 10 μmol/kg and thus could not be included in the regression analysis. In addition, there are three drugs, 3,4-DMA, 3,4-MDA and PMA (filled triangles, fig. 9), which are more potent in reducing responding under the FR schedule

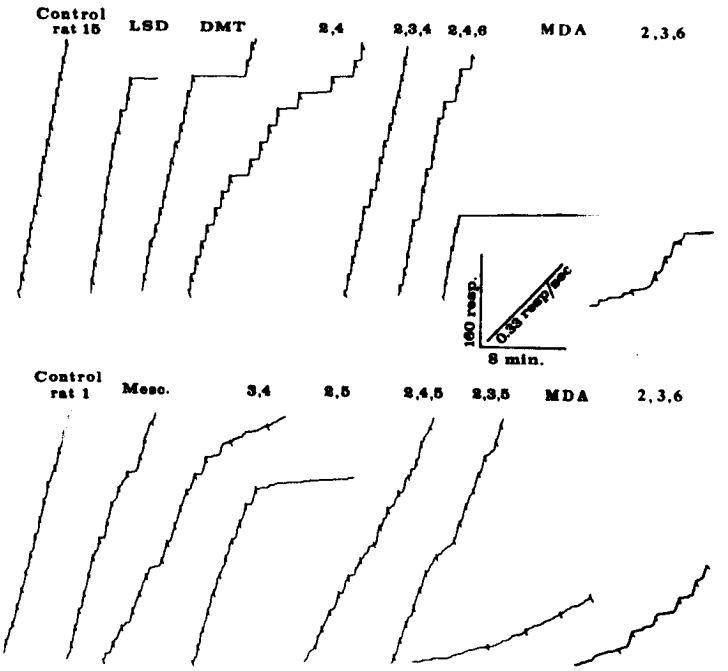

FIG. 5. FR cumulative records of two animals after administration of several drugs. Abscissa represents time and the ordinate represents cumulative responses as shown in inset. Vertical deflection of the recorder pen indicates presentation of food pellets. The dosages used (milligrams per kilogram) were: LSD, 0.1; DMT, 10; 2,4-DMA, 3; 2,3,4-TMA, 10; 2,4,6-TMA, 3; mescaline, 30; 3,4-DMA, 10; 2,5-DMA, 10; 2,4,5-TMA, 3; 2,3,5-TMA, 30; 3,4-MDA, 3; 2,3,6-TMA, 30.

in the rat than would be predicted from their activity in humans. Comparing the absolute potencies of the drugs, similar doses of PMA and MDA, on a micromole per kilogram basis, were required to produce effects in both humans and rats, whereas for most of the other drugs about 10 times higher dosages were required in the rat even though the drugs were administered orally to the human subjects (except for DMT which was given intramuscularly, because it is inactive orally), whereas they were administered s.c. or i.p. to the rats. One of these drugs, 2,3,4-TMA, was found to be inactive in humans (Shulgin *et al.*, 1969) and was found to be about as active as mescaline in disrupting responding in rats, indicating that it should be active in humans at about 20 μmol/kg. Since the highest dose tested in humans was 10 μmol/kg, and this dose was inactive, this drug could not be included in the correlation analysis. The correlation analysis presented in figure 9 for responding under the FR schedule relies heavily on the values for LSD because it is much more potent than the other drugs. However, for responding under the FI schedule values for two other potent hallucinogens, R- and R,S-DOM (2,5-dimethoxy-4-methylamphetamine) were determined (Harris *et al.*, 1977b) and these values were added to those determined in the present studies (fig. 9, upper panel). In this case, the value for LSD may be eliminated and the remaining points are significantly ($P < .01$) correlated with a straight line.

It has been suggested (Barfknecht *et al.*, 1975) that the differences in potency among the methoxylated amphetamines are related to their lipophilicity (as indicated by their octanol-water partition coefficients) and may merely reflect differences in penetration of the blood-brain barrier. However, the FI or FR ED50 values obtained in this study are not correlated ($r = 0.3$, $n = 10$) with the octanol-water partition coefficients of these drugs as determined by Barfknecht *et al.* (1975). For example, methoxylation of PMA to give 2,4-DMA results in a 3-fold decrease in behavioral activity, but the octanol-water partition coefficients of the two compounds are equal. However, differences in lipid solubility may be

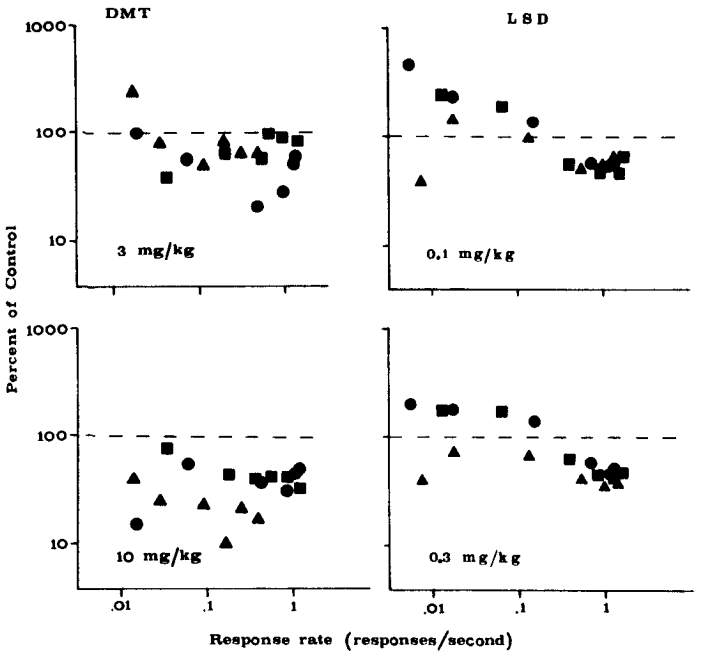

FIG. 6. Effects of DMT and LSD on local rates (successive sixths of the FI) of responding plotted as a function of the control rate of responding (abscissa). The dashed line at 100% of control rate indicates no change from the control data. Each of the symbols (square, circle or triangle) represents duplicate determinations in an individual animal. Linear regression lines were fitted to the points and data derived from these lines are presented in table 2.

important for the potency differences between some of the compounds. This is illustrated by MDA, which is about 5 times more potent than the structurally similar 3,4-DMA and is also 5 times more lipid soluble than 3,4-DMA. In addition to the potency differences between these two drugs, MDA was found to produce rate-dependent effects, whereas 3,4-DMA was not (see below), and this difference is likely due to chemical properties other than lipid solubility.

Under the FR schedule, LSD and several other hallucinogens decreased the rate of responding by producing very long postreinforcement pauses with near normal rates of responding occurring before and after these pauses. This result confirms earlier reports (Freedman *et al.*, 1967; Appel, 1968) of this effect of LSD on FR responding and extends these observations to include four other hallucinogens. However, a number of other hallucinogens did not produce this sudden cessation of responding in all animals but rather produced slower and more erratic responding throughout each ratio for some animals. Thus, no distinctive or consistent effects on FR responding could be attributed to the hallucinogens as a group.

Examination of the effects of all 16 drugs on the local rates of FI responding indicated that only *d*-amphetamine, MMA, PMA, LSD and MDA produced clear rate-dependent effects in all animals tested. These drugs increased responding at the beginning of the interval where the control rate of responding was low, and decreased responding later in the interval where the control rate of responding was higher. This is in agreement with other reports of the effects of *d*-amphetamine (Clark and Steele, 1966) and of LSD (Appel, 1971; Dykstra and Appel, 1972; Altman and Appel, 1975). One other hallucinogen, DOM, also has been shown to produce rate-dependent effects on responding under an FI schedule (Tilson *et al.*, 1975a, Harris *et al.*, 1977b). Although mescaline has been reported to increase low rates of responding (Tilson and Sparber, 1973), it was not found to produce rate-dependent effects in this study or in a study by McMillan (1973) using a FI 5 schedule with pigeons. Except for *d*-amphetamine, PMA, MMA, LSD and MDA, the drugs in this study generally decreased the rate of responding throughout the interval, although with some animals there were rate increases seen with several of the drugs.

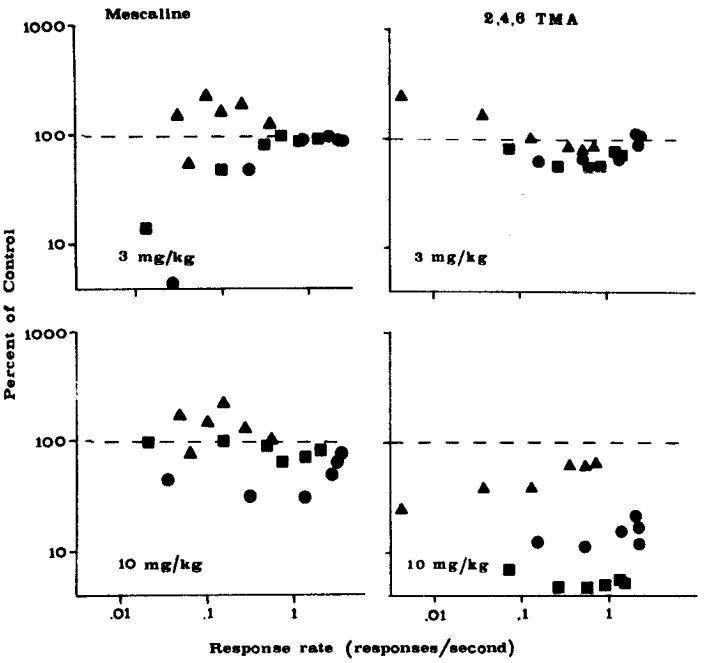

FIG. 7. Effects of mescaline and 2,4,6-TMA on local rates (successive sixths of the FI) of responding plotted as a function of the control rate of responding (abscissa). The dashed line at 100% of control rate indicates no change from the control data. Each of the symbols (square, circle or triangle) represents duplicate determinations in an individual animal. Linear regression lines were fitted to the points and data derived from these lines are presented in table 2.

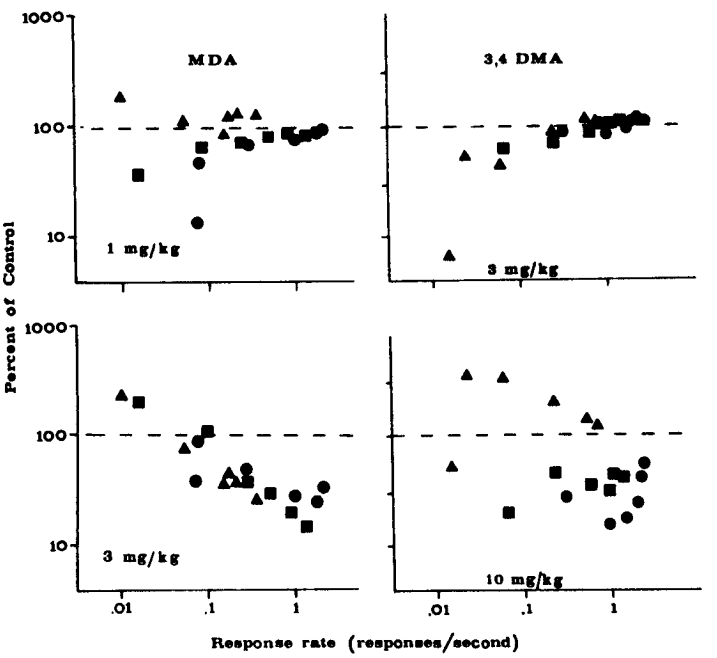

FIG. 8. Effects of 3,4-MDA and 3,4-DMA on local rates (successive sixths of the FI) of responding plotted as a function of the control rate of responding (abscissa). The dashed line at 100% of control rate indicates no change from the control data. Each of the symbols (square, circle or triangle) represents duplicate determinations in an individual animal. Linear regression lines were fitted to the points and data derived from these lines are presented in table 2.

TABLE 2

Data derived from regression lines fitted to log control response vs log percent of control rate for FI responding

Examples of these data are presented in figures 8, 9 and 10. Regression lines were fitted to the data for each animal by the method of least squares and the data presented below are means of the values from three animals.

Drug	Dose	Slope	y-Intercept (y as % of x, when x = 1 response/sec)	Correlation Coefficient (absolute value)
	mg/kg	*degrees*		
LSD	0.03	−3.2 (−10 to 4)	101 (68-135)	0.50
	0.1	−14.3 (−20 to −8)	60 (28-92)	0.69
	0.3	−12.6 (−19 to −7)	50 (21-80)	0.77
DMT	1	−4.2 (−11 to 3)	84 (50-129)	0.63
	3	−5.0 (−11 to 1)	56 26-87)	0.74
	10	−6.5 (−12 to 1)	30 (1-60)	0.73
Mescaline	3	14.1 (8 to 20)	128 (98-158)	0.71
	10	1.0 (−6 to 8)	81 (42-120)	0.55
	30		No responding	
MDA	1	8.4 (1 to 15)	90 (59-121)	0.78
	3	−25.0 (−19 to −30)	21 (1-40)	0.91
3,4-DMA	3	14.8 (9 to 21)	120 (95-145)	0.89
	10	7.1 (0 to 14)	80 (46-114)	0.43
2,4-DMA	3	6.7 (1 to 13)	126 (95-155)	0.69
	10	−5.7 (−13 to 1)	35 (1-69)	0.59
2,5-DMA	3	5.5 (−2 to 13)	83 (43-122)	0.44
	10	−9.8 (−17 to 2)	48 (8-88)	0.40
2,4,5-TMA	1	3.7 (−3 to 10)	85 (56-119)	0.67
	3	−10.0 (−17 to −2)	47 (12-82)	0.63
2,4,6-TMA	1	−1.9 (−8 to 4)	85 (55-115)	0.74
	3	4.3 (−2 to 10)	72 (38-106)	0.67
	10	5.3 (−3 to 12)	29 (0-65)	0.55
2,3,6-TMA	3	11.6 (5 to 18)	99 (69-128)	0.85
	10	16.3 (9 to 23)	69 (28-110)	0.55
	30	−2.2 (−8 to 4)	22 (0-51)	0.83
2,3,5-TMA	10	0.8 (−6 to 8)	85 (46-126)	0.50
	30	16.9 (8 to 25)	12 (0-40)	0.88
2,3,4-TMA	10	−1.2 (−8 to 6)	83 (45-120)	0.56
	18	9.9 (1 to 19)	33 (0-74)	0.36

It should be noted that MMA did not increase the low rates of responding found immediately after reinforcement as much as would be expected from the rate-dependent formulation. This may be due to a modulation of the drug effect by the strong stimulus control exerted by reinforcement presentation, which would be in keeping with the observation that the degree of stimulus control can modulate the rate-dependent effects of some drugs, such as chlorpromazine, without altering the rate-dependent effects of other drugs, such as *d*-amphetamine (Leander and McMillan, 1974).

Since PMA, MDA and LSD produced rate-dependent effects, while the other hallucinogens did not, it is pertinent to note other differences which have been observed among the various hallucinogens. Although not carefully studied, some of the subjective effects of LSD (such as euphoria and alertness) are similar to those of amphetamine (Rosenberg *et al.*, 1963), and the effects of LSD reportedly can be distinguished from those of mescaline (Shulgin and Carter, 1975). MDA produces some amphetamine-like effects, such as euphoria and stimulation and lacks the pronounced hallucinogenic activity of the methoxylated amphetamines (Snyder *et al.*, 1968; Shulgin, 1973a). The variety of subjective effects produced by these drugs in humans may be related to results showing that rats can be trained to discriminate between LSD and mescaline (Cam-

eron and Appel, 1973) and that DOM appears to have some of the stimulus properties of both mescaline (Winter, 1975) and *d*-amphetamine (Tilson *et al.*, 1975b). Thus the "hallucinogens" do not represent a completely homogeneous group in terms of their effects on responding under FI and FR schedules, their subjective effects in humans or their stimulus properties in animals.

The neurochemical effects of amphetamine derivatives recently have attracted a good deal of attention, and it is of interest to compare their potencies in decreasing responding under FI and FR schedules (*d*-amphetamine > PMA > MMA > OMA) with their neurochemical actions. For example, low concentrations (10^{-6} *M*) of *d*-amphetamine increased the release and inhibited the uptake of norepinephrine (NE) and dopamine, while similar concentrations of PMA altered the release and uptake of NE and 5-HT (Tseng *et al.*, 1976). By comparison, MMA was less potent than *d*-amphetamine or PMA in releasing NE, was less potent than *d*-amphetamine in releasing or blocking the uptake of dopamine and was less potent than PMA in releasing or blocking the uptake of 5-HT. This is in agreement with the higher potency of amphetamine and PMA and the low potency of MMA in decreasing the average rates of responding under both the FR and FI schedules of food presentation. Higher concentrations of OMA (>10^{-4} M) were required to produce alterations of neurotransmitter function similar to those produced by lower concentrations of MMA. This correlates with the very low potency of OMA in reducing rates of responding under the FR and FI schedules and its lack of effect on locomotor activity, body temperature and myoclonic twitch activity (Menon *et al.*, 1976).

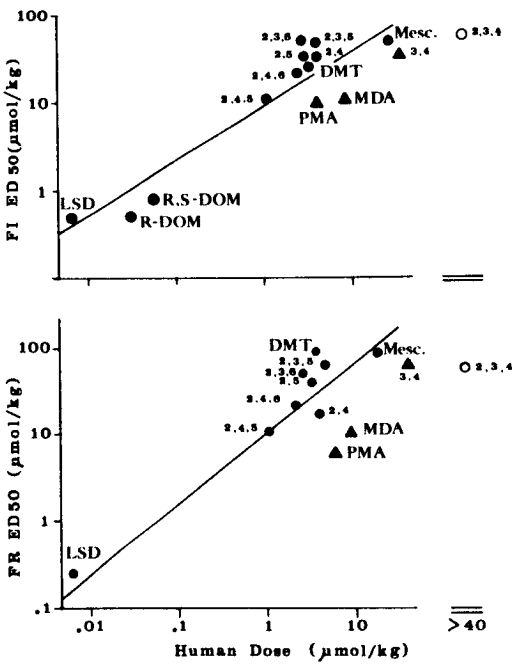

FIG 9. Correlation of potencies of the drugs in producing subjective effects in humans with their potencies in reducing average rates of responding under FI and FR schedules. FI and FR ED50 values are the doses of the drugs required to reduce responding to 50% of the control rate as calculated from data such as those shown in figure 4. All doses are calculated as the free base of the drug. Human doses were calculated from Rosenberg *et al.* (1963); Shulgin (1973a,b) and Wyatt *et al.*(1974). FI ED50 values for R- and R,S-DOM are from Harris *et al.* (1977b). In human studies all drugs were administered p.o. except DMT which was given i.m. In the rat studies LSD, PMA and DMT were given s.c., while the remaining drugs were injected i.p. Correlation coefficients and significance levels are: for drugs represented by filled circles or triangles, FI, $n = 14$, $r = 0.89$, $P < .001$; FR, $n = 12$, $r = 0.80$, $P < .01$; for drugs represented by filled circles, FI, $n = 11$, $r = 0.95$, $P < .001$; FR, $n = 9$, $r = 0.94$, $P < .001$.

The rate-dependent effects observed in this study and in others may also reflect neurochemical similarities between these various drugs. For example, *d*-amphetamine, MMA and PMA all produced rate-dependent effects and all have been shown to affect brain catecholamine systems. In other studies, cocaine and methylphenidate also produced pronounced rate-dependent effects (Smith, 1964; Harris *et al.*, 1977a) and these drugs are known to inhibit the uptake of catecholamines. In addition, the hallucinogenic amphetamine derivative, DOM, also has been shown to produce rate-dependent effects and to release brain catecholamines (Vrbanac *et al.*, 1975; Harris *et al.*, 1977b), whereas mescaline does not appear to produce rate-dependent effects or to release brain norepinephrine (Tilson and Sparber, 1972). The two other hallucinogens which were found to be rate dependent, LSD and MDA, have been reported to stimulate central dopamine receptors (Pieri *et al.*, 1974; von Hungen *et al.*, 1974, 1975; Da Prada *et al.*, 1975; Costall and Naylor, 1975), while mescaline and DMT do not produce this effect (von Hungen *et al.*, 1975). The effects of various hallucinogens on serotonergic systems are more consistent as

LSD, mescaline, DMT and DOM all appear to stimulate serotonin receptors (Aghajanian *et al.*, 1970; Haigler and Aghajanian, 1974). It has been suggested that these serotonergic effects are involved in the disruption of schedule-controlled responding by hallucinogens as pretreatment with a serotonin receptor blocker, cinanserin, prevented the rate-decreasing effects of five hallucinogens under a FR 30 schedule (Rech *et al.*, 1975). These results suggest that a number of hallucinogens stimulate serotonergic receptors, whereas six of the drugs studied (*d*-amphetamine, MMA, PMA, MDA, LSD and DOM) have more pronounced effects on central catecholamine systems than drugs such as mescaline and DMT. Taken together with the observations that *d*-amphetamine, MMA, PMA, MDA, LSD and DOM produced rate-dependent effects while other drugs such as mescaline and DMT did not produce these effects, these data suggest that rate-dependent effects may be produced by activation of catecholamine systems and inhibited by stimulation of serotonergic systems. However, further experiments are required to prove a causal relationship between these biochemical and behavioral effects.

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