Neuropharmacology Vol. 25, No. 10, pp. 1127–1135, 1986
Printed in Great Britain

0028-3908/86 $3.00 + 0.00
Pergamon Journals Ltd

SOME EFFECTS OF *d*-AMPHETAMINE, CAFFEINE, NICOTINE AND COCAINE ON SCHEDULE-CONTROLLED RESPONDING OF THE MOUSE

J. R. GLOWA*
Laboratory of Psychobiology, Department of Psychiatry, Harvard Medical School, Boston, MA 02115, U.S.A.

(*Accepted* 26 *December* 1985)

Summary—The effects of *d*-amphetamine (0.03–10.0 mg/kg), caffeine (0.3–100.0 mg/kg), nicotine (0.003–10.0 mg/kg) and cocaine (0.03–56.0 mg/kg) were compared on responding maintained under three different schedules of food presentation in mice. Cumulative doses of *d*-amphetamine, nicotine and cocaine only decreased responding maintained under fixed-ratio 30 response, fixed-interval 60-sec and fixed-interval 60-sec schedules with a punishment contingency (suppressed responding). In most cases there was an inverse relationship between the ED_{50} (dose which decreased responding by 50%) for the drug and the rate of responding maintained under each schedule. The exceptions were, (i) with both *d*-amphetamine and cocaine the ED_{50} for suppressed responding was smaller than that for non-suppressed fixed-interval responding, and (ii) with nicotine the ED_{50} for fixed-ratio responding was smaller than that for fixed-interval responding. In contrast, intermediate doses of caffeine increased suppressed responding, had little effect on fixed-interval responding and decreased fixed-ratio responding. This difference in profile of effect over the range of conditions studied, suggests that the behavioral effects of psychomotor stimulants can be used to examine potential differences in the mechanisms of action of each drug. Such findings may aid in the understanding of the relationships between the neuropharmacological and behavioral effects of psychomotor stimulant drugs.

Key words: *d*-amphetamine, caffeine, nicotine, cocaine, schedule-controlled behavior, fixed-interval, fixed-ratio, suppressed responding, mice.

The behavioral effects of psychoactive drugs often depend upon the specific properties of the behavior that is studied. For learned behavior a relationship between the normally occurring rate of behavioral response and the effect of the drug has been established (Dews, 1958). These effects which are rate-dependent are different for different classes of drugs (Dews and DeWeese, 1977). For drugs with psychomotor stimulant properties, responding that normally occurs at a low rate can be increased by the same dose that will only decrease responding which occurs at higher rates (Kelleher and Morse, 1968). When responding is maintained under comparable conditions (i.e. same rate of responding, maintaining events, etc.) the behavioral effects of different psychomotor stimulants can often appear to be similar. However, few studies have directly compared the rate-dependent effects of these drugs over a range of conditions. There is reason to believe that while the behavioral effects of psychomotor stimulants are similar under some conditions, they can be quite different under others. For example, *d*-amphetamine and caffeine both increase responding maintained under conditions resulting in low rates of responding while decreasing responding maintained under conditions resulting in higher rates (Davis, Kensler and Dews, 1973). When these drugs were directly compared under two conditions that maintained different rates of responding, there was a large difference in their potencies for increasing rates, but not in their efficacy in decreasing rates (McKim, 1980).

Since most studies of the behavioral effects of psychomotor stimulants have focused on their rate-increasing effects, the present study was designed to compare the effects of several of these drugs on responding maintained under a range of conditions which normally result in rate-decreasing effects. Such effects are of interest, not only because they can occur at doses similar to those having stimulant effects, but also because they represent a drug-induced decrement in normal behavioral functioning. When the effects of *d*-amphetamine, cocaine, caffeine and nicotine were compared, in most cases a similar quantitative relationship was found between the dose which decreased responding by 50% (ED_{50}) and the rate of responding under each condition. In addition, qualitative differences in effects were also seen, particularly with caffeine. The results emphasize that both qualitative and quantitative differences in the behavioral effects of psychomotor stimulants can be obtained which depend upon the conditions under

*Present address: Clinical Neuroscience Branch, NIMH, Bethesda, MD 20205, U.S.A.

which responding is maintained, and suggest that studies relating neuropharmacological indices to behavioral effects examine the role of these conditions as well.

METHODS

Subjects

Adult male experimentally naive mice, derived from the Charles River CD-1 strain, were used. At the beginning of the study, mice weighing 35.0 g were selected and then deprived of food to 80% of that weight (28.0 g).

Apparatus

Mice were studied individually in four black plexiglas operant chambers (10 cm × 13 cm deep × 10 cm high), similar to those described by Glowa, DeWeese, Natale, Holland and Dews (1983). Behind the front wall of each chamber, a photocell and light source were mounted opposite each other, horizontally, 1.2 cm above the floor. A 0.5-cm hole through the front wall allowed the interruption of the light upon the photocell. Each interruption defined a response, and operated programming and recording equipment and an a.c. feedback relay located on the chamber. A 0.025 ml food dipper could be raised through the floor, permitting access to evaporated milk. A white lamp (7.5 W, 115 V a.c.) and white masking noise served as discriminative stimuli. Electric shocks (650 V a.c., 40 msec, 0.3 mA) were delivered to the front plate and floor bars through a BRS Foringer Grid Shock Scrambler. Operant chambers were contained within sound-attenuating, ventilated enclosures.

Procedure

The mice were deprived of food for 2 days and then trained under a fixed-interval 60-sec schedule of presentation of food (see below). When responding was well maintained, the mice were arbitrarily assigned to a group that was trained under the schedule conditions described below. Experiments were conducted for 5 days a week.

Schedules

Fixed-interval 60-sec. Under the fixed-interval the first response to follow a 60-sec interval produced immediate access to food for 4 sec. Under the fixed-ratio 30-response schedule each 30th response produced access to milk. Under another condition a fixed-interval 60-sec schedule maintained responding and, in addition, each 15th response produced a shock [fixed-interval 60-sec (fixed-ratio 15-shock)]. The response which produced food could not produce shock; the fixed-ratio re-started at the beginning of each interval.

Under each schedule, presentation of food was followed by a 5-sec interval during which responding had no scheduled consequences. Experimental sessions consisted of alternating periods of food-availability under the schedule (a "series") and a 300-sec between-series interval. Ten presentations of food per series were available under both fixed-interval schedules; 20 presentations of food per series were available under the fixed-ratio schedule. When each schedule was in operation a white stimulus lamp was on and white noise was off; at all other times white noise was on and the lamp was off.

The effects of each drug were studied by obtaining a cumulative dose–effect function. During a session with drugs the animal was first injected intraperitoneally with 0.2 ml saline solution, then placed in the chamber for 300-sec before the first series began. Shortly after the end of the first series the mouse was withdrawn, injected with the smallest dose studied and replaced into the chamber. After the completion of the next series the animal was again withdrawn and injected with enough drug to bring the cumulative dose up to the next largest selected dose, and replaced. This procedure was repeated until the series following the largest dose to be injected (usually that which completely eliminated responding) was completed. Sessions were usually terminated only after the complete elimination of responding. Sessions with drugs were typically eight series long, although the length of sessions could vary, depending upon the dose required to eliminate responding in individual mice. *d*-Amphetamine, caffeine, nicotine and cocaine were studied in that order.

Drugs

Anhydrous caffeine, cocaine hydrochloride, *d*-amphetamine sulfate (Sigma, St Louis, Missouri, U.S.A.) and nicotine hydrogen bitartrate (B.D.H., London) were dissolved in normal saline and diluted serially so the dose was contained in a volume of 5 ml/kg body weight.

Analysis of data

Overall rates of responding were calculated by dividing the total number of responses by the elapsed time during the operation of the schedule. The average time until the first response (pause time) under the fixed-ratio schedule is reported for the cumulative dose–effect data. At least two separate cumulative determinations for each drug were completed (except for animal M-305 with cocaine, when only one curve was obtained). Data are also expressed as the mean effect. Control values were obtained from the day before injection and from a series with injections of saline. The ED_{50} values (the dose required to decrease responding by 50%) were determined by fitting a straight line (linear regression) over the portion of the dose-effect function from the largest dose to produce less than a 20% decrease to the smallest dose to produce more than an 80% decrement in responding; from these functions the mean dose expected to produce a 50% decrement in responding (ED_{50}) was calculated.

RESULTS

Fixed-interval 60-sec

Rates and patterns of responding were comparable to those of earlier reports of responding maintained under similar conditions in other species (Ferster and Skinner, 1957; Harris, Snell and Loh, 1978; Zuccarelli and Barrett, 1980) and in the mouse (Glowa *et al.*, 1983). Rates of responding for individual mice ranged from 0.86 to 1.66 responses/sec. Experiments with drugs were begun when variability decreased to less than 20%.

Figure 1 shows the effects of the four drugs on performance maintained under the fixed-interval schedule. *d*-Amphetamine had little effect on responding at doses of 0.03–0.3 mg/kg; responding was decreased to about 50% of control values by 3.0 mg/kg, and 10.0 mg/kg usually abolished responding. Only caffeine increased responding at doses of 1.0–3.0 mg/kg, an effect due mostly to one mouse, and decreased responding at 30.0 mg/kg. Doses of 100.0 mg/kg abolished responding. Nicotine decreased responding at doses of 0.003 to over 10.0 mg/kg. The largest dose studied

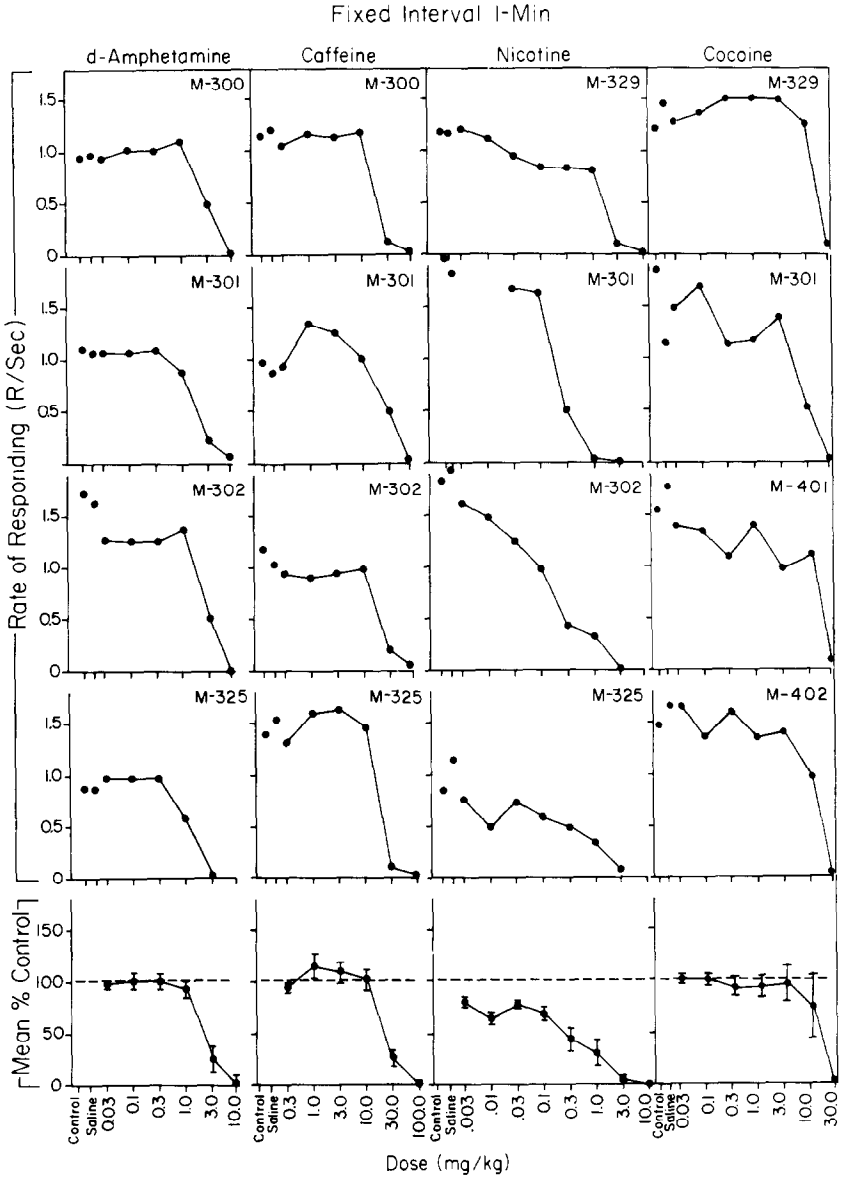

Fig. 1. Individual rates of responding and mean (±SEM) effect, plotted as a function of dose for *d*-amphetamine, caffeine, nicotine and cocaine, when the responding of mice was maintained under a fixed-interval 60-sec schedule of food presentation. Individual curves reflect at least two separate determinations. Saline represents responding during the first series of days with drugs; control represents overall rates on (non-injection control) days prior to days on drugs. Doses were obtained by injecting enough drug during the 5-min interval prior to each series, in order to increase the dose to the amount shown. The mean percentage control plots were obtained by comparing the effect of each dose to saline and non-injection controls for individual determinations, then averaging for determinations and animals.

(10.0 mg/kg) occasionally killed mice. Cocaine did not decrease responding at doses less than 3.0 mg/kg; however rate-decreasing effects were evident at 10.0 mg/kg for some mice and a 30.0 mg/kg in all the mice.

Fixed-ratio 30

Rates and patterns of responding under the fixed-ratio schedule were also similar to those of previous reports (Wenger, 1980). Responding was characterized by a brief period of no responding (pause) of about 1.6 sec at the beginning of each ratio; the overall rate of responding varied from about 2–5 responses/sec. Experiments with drugs were begun when the variability decreased to less than 20%.

Figure 2 shows the effects of the four psychomotor stimulants on responding maintained under the fixed-ratio schedule. Each drug decreased responding under the fixed-ratio 30 schedule in a dose-dependent manner; *d*-amphetamine decreased the rate of responding at doses of 0.3 mg/kg and responding was

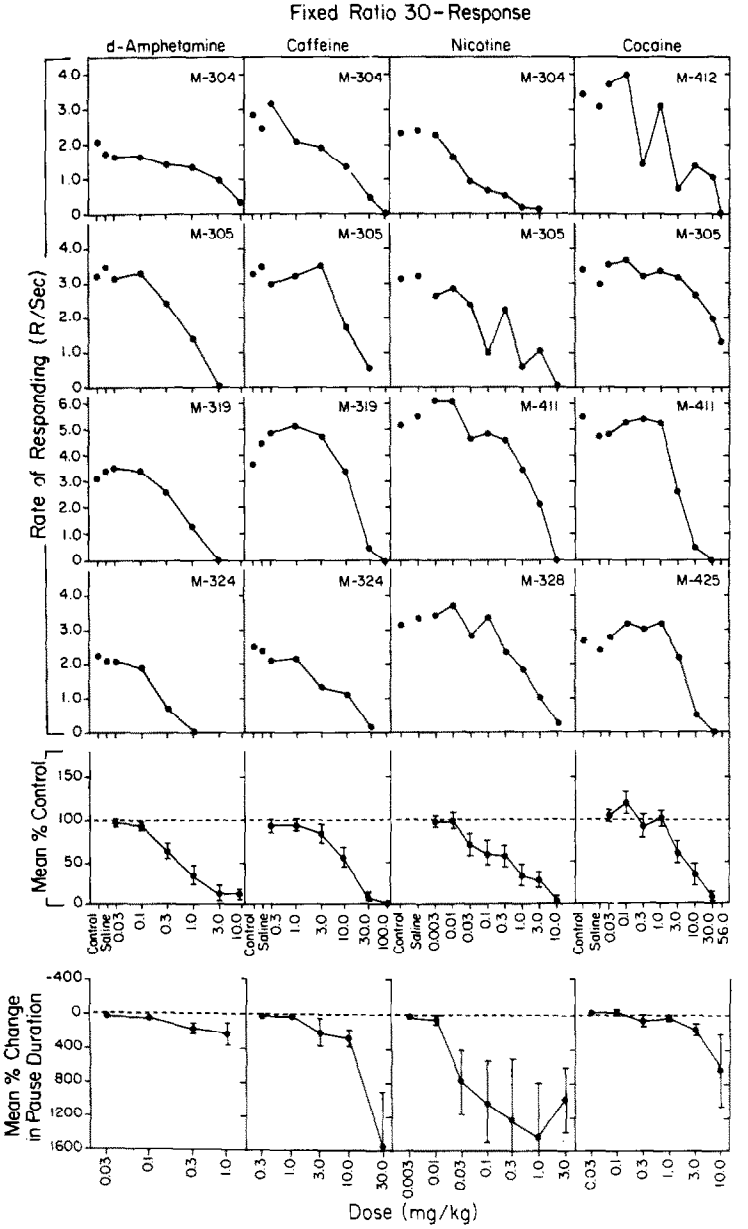

Fig. 2. Individual rates of responding and mean (±SEM) effect on rate (second from bottom graph) and on pause duration (bottom graph) plotted as a function of the dsoe for *d*-amphetamine, caffeine, nicotine and cocaine when the responding of mice was maintained under a fixed-ratio 30-response schedule of food presentation. Details as in Fig. 1. Durations of pauses from series that were terminated manually due to a lack of responding, as well as for doses with less than five determinations, are excluded.

abolished at 3.0 mg/kg. Decreases in rate after caffeine were evident in all mice at a dose of 10.0 mg/kg; responding was decreased almost completely by 30.0–100.0 mg/kg caffeine. Nicotine decreased rates of responding under the fixed-ratio schedule at doses greater than 0.01 mg/kg; responding was abolished at 10.0 mg/kg. Cocaine did not decrease responding at doses up to 0.1 mg/kg; 3.0 mg/kg usually decreased responding and doses as large as 30.0 mg/kg were required to abolish responding.

The lower panel in Fig. 2 shows that durations of pauses under the fixed-ratio 30-response schedule only increased with increasing doses of each drug. With the exception of nicotine, duration of pauses changed less than 4-fold at doses that decreased responding less than 50%. With nicotine, large increases in the variability of duration of pauses occurred at relatively small doses (0.03 mg/kg).

Fixed-interval (fixed-ratio 15 shock)

Rates of suppressed responding under the fixed-interval 60-sec schedule with fixed-ratio 15 shock-presentation ranged from 0.15 to 0.4 responses/sec. These rates were approx. 25% of those occurring before the shock was introduced. Experiments with drugs were begun when the variability decreased to less than 30%.

Figure 3 shows the effects of the four drugs studied on suppressed responding. While small doses of

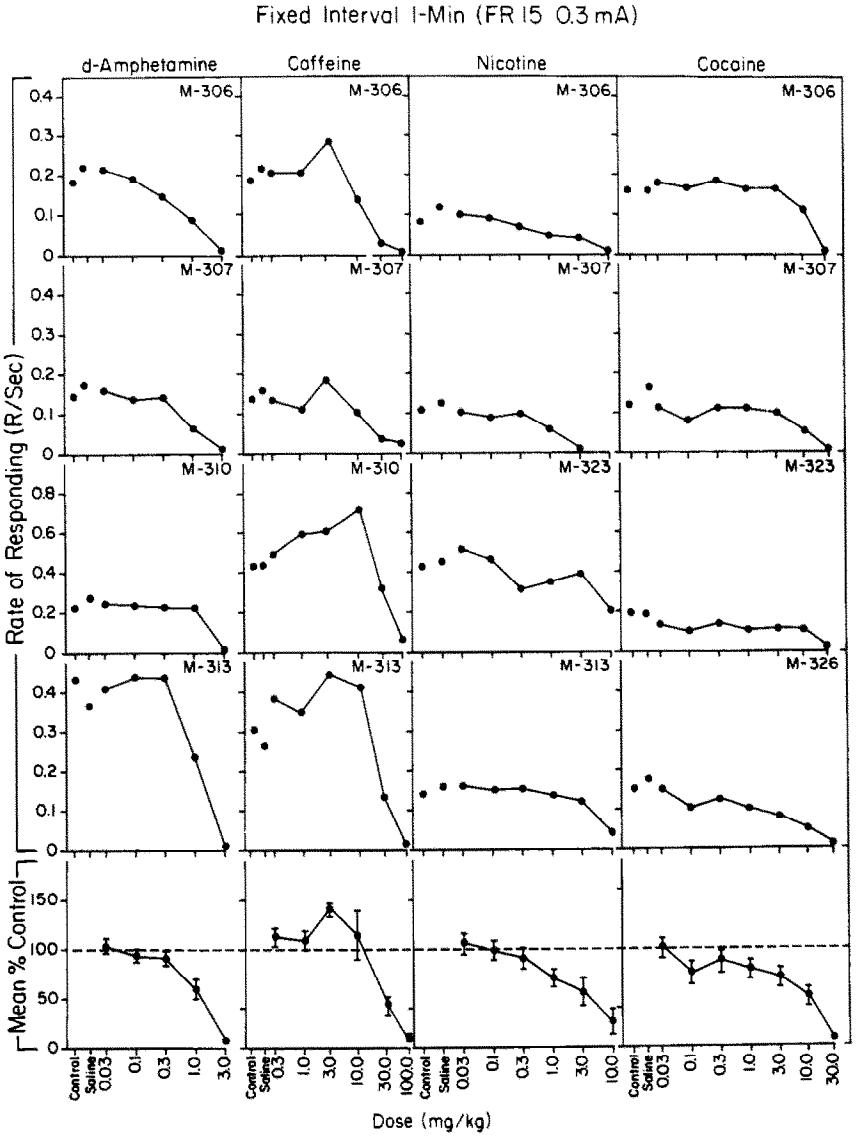

Fig. 3. Individual and mean (±SEM) dose–effect curves for *d*-amphetamine, caffeine, nicotine and cocaine on rates of responding of mice maintained under a fixed-interval 60-sec schedule of food presentation where each 15th response produced a 0.3 mA electric shock. Details as in Fig. 1.

Table 1. The mean dose (±SEM) of *d*-amphetamine, caffeine, nicotine or cocaine, in mg/kg, that reduced responding by 50% (ED_{50}) under the indicated schedule of reinforcement

	Schedule		
	Fixed-interval + shock	Fixed-interval 60-sec	Fixed-ratio 30
d-Amphetamine	1.07 (0.18)	2.18 (0.44)	1.00 (0.37)
Caffeine	35.50 (7.79)	23.80 (3.19)	10.60 (2.32)
Nicotine	3.01 (1.09)	0.36 (0.19)	0.71 (0.29)
Cocaine	9.60 (2.57)	13.47 (2.97)	12.00 (2.50)

d-amphetamine had no effect, intermediate doses decreased responding; 3.0 mg/kg abolished responding completely. Caffeine slightly increased responding at intermediate doses (1.0–10.0 mg/kg) and maximally increased responding 140 to 180% of control rates at 3.0 mg/kg. Responding was decreased by doses larger than 30.0 mg/kg. Neither nicotine nor cocaine increased suppressed responding; however for both of these drugs responding was gradually reduced, as a function of increasing dose, over a wide range of doses. For example, the largest dose of nicotine studied (10.0 mg/kg) failed to abolish responding.

Comparisons between cumulative dose–effects

Table 1 shows the mean ED_{50} values for each drug under each condition. In most cases there was an inverse relationship between the ED_{50} for the drug under a particular condition and the rate of responding maintained under that condition. For *d*-amphetamine, cocaine and caffeine the higher the rate of responding maintained by the schedule, the smaller the ED_{50}, except with both *d*-amphetamine and cocaine smaller doses decreased suppressed responding than those decreasing non-suppressed responding. With nicotine, while the ED_{50} was greater for suppressed, as opposed to non-suppressed, fixed-interval responding, the ED_{50} for fixed-ratio responding was intermediate. The ED_{50} for cocaine was approx. 10 mg/kg more than the dose of *d*-amphetamine required to produce the same effect.

DISCUSSION

The present study compared the behavioral effects of four psychomotor stimulants under three different conditions. With the exception of caffeine, each drug only decreased the overall rate of responding under each condition studied. In previous studies, these drugs have often produced rate-increasing effects. For example, when responding has been maintained under longer fixed-interval schedules or fixed-ratio schedules with large response requirements, these drugs characteristically increased overall rates of responding (Kelleher and Morse, 1968; McKim, 1980; McMillan, 1969). However, in experiments where responding has been maintained under shorter fixed-interval schedules or fixed-ratio schedules with smaller response requirements, these drugs have only decreased responding (Harris *et al.*, 1978; Heffner, Brawbaugh and Zigmond, 1974; McKim, 1980; McMillan, 1969; Zucarrelli and Barrett, 1980). A considerable body of data now supports the idea that the rate of responding controlled by such schedules is an important variable in modulating the behavioral effects of these drugs (Dews, 1958; Kelleher and Morse, 1968; McKearney and Barrett, 1978; Sanger and Blackman, 1976). In particular, there appears to be a linear inverse relationship between the rate of responding and the ability of these drugs to increase responding. Higher rates of responding are less likely to be increased, if at all, while lower rates of responding are readily increased. Thus, the rate-decreasing effects found are consistent with what would be expected on the basis of rate-dependency for the relatively high rates of responding studied.

The present experiments offer a more detailed analysis of these rate-decreasing effects by attempting to relate the effect of each drug to the overall rate of responding maintained over a limited range of conditions. For example, the rate of responding under the punishment condition was uniformly lower than that under the same schedule of food presentation, when responding was not suppressed, and the rate of responding under the fixed-interval schedule was uniformly lower than that under the fixed-ratio schedule. The rate-decreasing effect of each drug was also different under each of the three schedules studied. For caffeine the ED_{50} was greatest for suppressed responding, intermediate for fixed-interval responding, and smallest for fixed-ratio responding. For *d*-amphetamine and cocaine a similar relationship was obtained for fixed-interval and fixed-ratio responding, and for nicotine a similar effect was obtained for suppressed and non-suppressed fixed-interval responding. This inverse relationship between the ED_{50} and the rate of responding under these conditions is consistent with the idea that the rate-decreasing effect of these drugs is related to the normally occurring rate of behavior. These findings are also consistent with those of two other experiments in which the rate-decreasing effects of some of these drugs were systematically compared. In one (Heffner *et al.*, 1974), a direct relationship was found between the rate-decreasing effect of *d*-amphetamine and the rate of responding maintained under six different schedule conditions. In the other (Harris *et al.*, 1978), the rate-decreasing effects of *d*-amphetamine, cocaine and caffeine were found to be greater under fixed-ratio schedules than under fixed-interval schedules. These findings are important because they

suggest that rate-dependent effects, similar to those which result in the difference between rate-increasing and rate-decreasing effects seen in widely discrepant conditions (i.e. long fixed-intervals and fixed-ratios with small response requirements), can also be seen over a limited range of conditions which result primarily in only rate-decreasing effects. Thus, the rate-decreasing effects of these drugs appear to be related to the same behavioral mechanism of action which results in their rate-increasing effects.

Three exceptions to this generality were observed. Two of these involved the failure of the ED_{50} dose for *d*-amphetamine and cocaine under the punishment condition to surmount that seen under the fixed-interval schedule. Previous reports have indicated that *d*-amphetamine and cocaine do not increase rates of suppressed responding (Geller and Seifter, 1961; Glowa and Barrett, 1983; McMillan, 1975; Spealman, 1979). In contrast to the rate-increasing effects typically seen on comparably low rates of non-suppressed responding, suppressed responding is decreased at smaller doses of these drugs than those required to decrease non-suppressed responding (Lazareno, 1979; Spealman, 1979). The increase in sensitivity of suppressed responding is an important exception to the manner in which the rate of responding is normally related to the behavioral effects of these drugs and appears to differentiate a unique property of *d*-amphetamine and cocaine. An increased sensitivity of punished responding to the rate-decreasing effects of other, non-psychomotor, stimulants of the central nervous system has been described recently (Corda, Blaker, Mendelson, Guidotti and Costa, 1983; Mendelson, Davis, Paul and Skolnick, 1983). Further research should assess the possibility that a unique neuropharmacological mechanism of action for stimulant-type drugs may be revealed by the use of suppressed responding.

The other exception to the general relationship observed was the failure of nicotine to decrease fixed-ratio responding at smaller doses than those decreasing fixed-interval responding. The effect of nicotine on fixed-interval and fixed-ratio responding was different from that of effects reported previously for the squirrel monkey (Spealman, Goldberg and Gardner, 1981). In that study the ED_{50} for fixed-interval (5-min) responding was larger than that for fixed-ratio 30 responding, in accordance with the general findings described here. Differences in either the species studied, or in factors related to the scheduling of events (the previous study used a multiple schedule while the current study used isolated schedules) may have contributed to these differences. However, nicotine also increased the variability in the duration of pauses of fixed-ratio responding to a much greater extent than the other drugs studied here. A recent study of the behavioral effects of nicotine, administered intraventricularly, showed that the durations of pauses increased under different fixed-ratio schedules in a manner that was inversly related to the rate of response, even though pauses were of similar duration under the different schedules (DeNoble, Dragon and Carron, 1982). Such results suggest that, under certain conditions, the dependence of the behavioral effects of nicotine on the rate of responding may be non-linear. An earlier study which showed that nicotine increased responding maintained under fixed-ratio schedules supports this possibility (Pradhan, 1970). Clearly, further research on the behavioral effects of nicotine is warranted.

The effects of caffeine were different from those of *d*-amphetamine and cocaine; not only did caffeine increase suppressed responding, as shown previously (Beer, Chasin, Clody, Vogel and Horovitz, 1972; Glowa and Spealman, 1984; Morrison, 1969; Valentine and Spealman, 1983), but larger doses were required to decrease suppressed responding. Non-suppressed responding was increased, but only clearly in one of the four mice studied. The difference in both the overall effect of caffeine on responding, and its ED_{50} as a function of the schedule controlling responding, is consistent with an effect dependent on rate. This conclusion is supported by previous reports of the rate-dependent effects of caffeine on non-punished responding (Davis *et al.*, 1973; Meliska and Brown, 1982; McKim, 1980). Thus, the increase in punished responding with caffeine does not represent an exception to rate-dependency similar to that observed with *d*-amphetamine and cocaine and clearly differentiates the behavioral effects of caffeine from those of other psychomotor stimulants. This increase is also of interest because similar effects on suppressed responding have been related to the anxiolytic effects of drugs (Sepinwall, 1983). Larger doses of caffeine have been used in clinical settings to produce self-reports of anxiety in human subjects (Greden, 1974), although this effect may be restricted to certain populations (Boulenger, Uhde, Wolff and Post, 1984). The current findings suggest that small doses of caffeine may exhibit an anxiolytic effect.

Some of the behavioral effects of psychomotor stimulants have been related to specific neuropharmacological effects. For example, the rate increasing effects of caffeine appear to be blocked by adenosine agonists (Snyder, Katims, Annau, Bruns and Daly, 1981; Glowa and Spealman, 1984) while the rate-decreasing effects are not (Glowa and Spealman, 1984; Glowa, Sobel, Malaspina and Dews, 1986). Both the rate-increasing and rate-decreasing effects of nicotine are blocked by the centrally-acting, cholinergic antagonist, mecamylamine (Spealman *et al.*, 1981; Morrison, Goodyear and Sellers, 1969). While the effects of cocaine have not been studied in combination with other drugs, the behavioral effects of *d*-amphetamine have been studied extensively. Chlorpromazine can block the rate-increasing effects of *d*-amphetamine (Brown, 1963; Davis, 1965), while reserpine enhances the rate increasing effects and blocks its rate-decreasing effects (Smith, 1964). How-

ever, Ganousis and Tessel (1981) reported that nisoxetine, an inhibitor of the uptake of norepinephrine, could also block the rate-increasing effects of *d*-amphetamine, while potentiating the rate-decreasing effects. Lazerno (1979) reported that the sensitivity of punished responding to the rate-decreasing effects of *d*-amphetamine could be attenuated by blockade of dopamine receptors, but not blockade of norepinephrine receptors. Thus, different neuropharmacological mechanisms may come into play when responding is controlled under widely different conditions.

While the behavioral effects of drugs with psychomotor stimulant properties may involve a variety of different neuropharmacological actions, they also depend upon the specific environmental conditions relating to the behavior under study. As it is these behavioral effects of psychomotor stimulants which are most likely to be related to their use (or abuse), their neuropharmacological effects may differ under conditions that result in different behavioral effects. This may be an important point in relating the neuropharmacological actions of drugs to different behavioral effects. For example, most psychomotor stimulants do not have comparable rate-increasing effects. Both nicotine (Spealman *et al.*, 1981) and caffeine (McKim, 1980) are less efficacious in increasing responding than *d*-amphetamine, while cocaine and analogs of cocaine are not (Spealman, Goldberg, Kelleher, Goldberg and Charlton, 1977). Rate-decreasing effects of drugs are also of interest, and, as all psychomotor stimulants can decrease responding to a comparable extent, these rate-decreasing effects may serve as a more practical measure by which comparisons can be made. The present study shows that different psychomotor stimulants decrease responding in different ways, and thus, may provide a unique way to dissociate neuropharmacological mechanisms of action related to the ability to disrupt behavior.

Acknowledgements—The present research was supported under USPHS Grants MH14275, OH00706, MH02094, DA00499, DA02658 and MH07658. The author gratefully thanks Dr J. E. Barrett and Dr P. B. Dews for helpful comments on an earlier version of the manuscript.

REFERENCES

Beer B., Chasin M., Clody D. E., Vogel J. R. and Horovitz Z. P. (1972) Cyclic adenosine monophosphate phosphodiesterase in brain: effect on anxiety. *Science* **176:** 428–430.

Boulenger J., Uhde T. W., Wolff E. A. and Post R. M. (1984) Increased sensitivity to caffeine in patients with panic disorders. *Archs gen. Psychiat.* **41:** 1067–1071.

Brown H. (1963) *d*-Amphetamine-chlorpromazine antagonism in a food-reinforced operant. *J. exp. Anal. Behav.* **6:** 395–398.

Corda M. G., Blaker W. D., Mendelson W. B., Guidotti A. and Costa E. (1983) Beta-carbolines enhance shock-induced suppression of drinking in rats. *Proc. natn. Acad. Sci. U.S.A.* **80:** 2072–2076.

Davis J. (1965) Antagonism of a behavioral effect of *d*-amphetamine by chlorpromazine in the pigeon. *J. exp. Anal. Behav.* **8:** 325–327.

Davis T. R. A., Kensler J. J. and Dews P. B. (1973) Comparison of behavioral effects of nicotine, *d*-amphetamine, caffeine and dimethylheptyl tetrahydrocannabinol in squirrel monkeys. *Psychopharmacologia* **32:** 51–65.

DeNoble V. J., Dragon Y. P. and Carron L. (1982) Behavioral effects of intraventricularly administered (−)nicotine on fixed ratio schedules of food presentation in rats. *Psychopharmacology* **77:** 317–321.

Dews P. B. (1958) Studies on behavior. IV. Stimulant action of methamphetamine. *J. Pharmac. exp. Ther.* **122:** 137–147.

Dews P. B. and DeWeese J. (1977) Schedules of reinforcement. In: *Principles of Behavioral Pharmacology: Handbook of Psychopharmacology* (Iversen L. L., Iversen S. D. and Snyder S. H., Eds), Vol. 7, pp. 107–150. Plenum Press, New York.

Ferster C. B. and Skinner B. F. (1957) *Schedules of Reinforcement.* Appleton–Century–Crofts, New York.

Ganousis L. G. and Tessel R. E. (1981) Interactions of catecholamine uptake inhibitors and receptor blockers with amphetamine induced changes in locomotion, stereotypy, and milk-maintained operant responding in mice. *Fedn proc. Fedn Am. Socs exp. Biol.* **40:** 276.

Geller I. and Seifter J. (1961) The effects of meprobamate, barbiturates, *d*-amphetamine and promazine on experimentally induced conflict in the rat. *Psychopharmacologia* **1:** 482–492.

Glowa J. R. and Barrett J. E. (1983) Response suppression by visual stimuli paired with post-session *d*-amphetamine injections in the pigeon. *J. exp. Anal. Behav.* **39:** 154–162.

Glowa J. R., DeWeese J., Natale M. E., Holland J. J. and Dews P. B. (1983) Behavioral toxicology of volatile organic solvents I. Methods: Acute effects. *J. Am. Coll. Toxic.* **2:** 175–185.

Glowa J. R. and Spealman R. D. (1984) Behavioral effects of caffeine, *N*6-(L-phenylisopropyl) adenosine and their combination in the squirrel monkey. *J. Pharmac. exp. Ther.* **231:** 665–670.

Glowa J. R., Sobel E., Malaspina S. and Dews P. B. (1986) Behavioral effects of caffeine, (−)-*N*6-[(*R*)-1-methyl-2-phenylethyl]-adenosine (PIA) and their combination in the mouse. *Psychopharmacology.* In press.

Greden J. F. (1974) Anxiety or caffeinism: A diagnostic dilemma. *Am. J. Psychiat.* **131:** 1089–1092.

Harris R. A., Snell D. and Loh H. H. (1978) Effects of stimulants, anoretics and related drugs on schedule-controlled behavior. *Psychopharmacology* **56:** 49–55.

Heffner T. G., Drawbaugh R. B. and Zigmond M. J. (1974) Amphetamine and operant behavior in rats: Relationship between drug effect and control response rate. *J. comp. physiol. Psychol.* **86:** 1031–1033.

Kelleher R. T. and Morse W. H. (1968) Determinants of the specificity of the behavioral effects of drugs. *Erge. Physiol. biol. chem. exp. Pharmak.* **60:** 1–56.

Lazareno S. (1979) *d*-Amphetamine and punished responding: the role of catecholamines and anorexia. *Psychopharmacology* **66:** 133–142.

Meliska C. J. and Brown R. E. (1982) Effects of caffeine on fixed-interval responding in the rat. *Pharmac. Biochem. Behav.* **16:** 745–750.

Mendelson W. B., Davis T., Paul S. M. and Skolnick P. (1983) Do benzodiazepine receptors mediate the anti-conflict action of pentobarbital? *Life Sci.* **32:** 2241–2246.

McKearney J. W. and Barrett J. E. (1978) Schedule-controlled behavior and the effects of drugs. In: *Contemporary Research in Behavioral Pharmacology* (Blackman D. E. and Sanger D. J., Eds), pp. 1–45. Plenum Press, New York.

McKim W. P. (1980) The effects of caffeine, theophylline and amphetamine on operant responding of the mouse. *Psychopharmacology* **68:** 135–138.

McMillan D. E. (1969) Effects of *d*-amphetamine on performance under several parameters of multiple fixed-ratio, fixed-interval schedules. *J. Pharmac. exp. Ther.* **167:** 26–33.

McMillan D. E. (1975) Determinants of drug effects on punished responding. *Fedn proc. Fedn Am. Socs exp. Biol.* **34:** 1870–1879.

Morrison C. F. (1969) The effects of nicotine on punished behavior. *Psychopharmacologia* **14:** 221–232.

Morrison C. F., Goodyear J. M. and Sellers C. M. (1969) Antagonism by antimuscarinic and ganglion-blocking drugs of some of the behavioral effects of nicotine. *Psychopharmacologia* **15:** 341–350.

Pradhan S. N. (1970) Effects of nicotine on several schedules of behavior in rats. *Archs int. pharmacodyn. Ther.* **170:** 264–275.

Sanger D. J. and Blackman D. E. (1976) Rate-dependent effects of drugs: a review of the literature. *Pharmac. Biochem. Behav.* **4:** 73–83.

Sepinwall J. (1983) Behavioral studies related to the neurochemical mechanisms of action of anxiolytics. In: *Anxiolytics: Neurochemical, Behavioral and Clinical Perspectives* (Malick J. B., Enna S. J. and Yamamura H. I., Eds), pp. 147–171. Raven Press, New York.

Smith C. B. (1964) Effects of *d*-amphetamine upon operant behavior in pigeons; enhancement by reserpine. *J. Pharmac. exp. Ther.* **146:** 167–174.

Snyder S. H., Katims J. J., Annau Z., Bruns R. F. and Daly J. W. (1981) Adenosine receptors and the behavioral actions of methylxanthines. *Proc. natn. Acad. Sci. U.S.A.* **78:** 3260–3264.

Spealman R. D., Goldberg S. R., Kelleher R. T., Goldberg D. M. and Charlton J. P. (1977) Some effects of cocaine and two cocaine analogs on schedule-controlled behavior of squirrel monkeys. *J. Pharmac. exp. Ther.* **202:** 500–509.

Spealman R. D. (1979) Comparison of drug effects on responding punished by pressurized air or electric shock delivery in squirrel monkeys: pentobarbital, chlordiazepoxide *d*-amphetamine and cocaine. *J. Pharmac. exp. Ther* **209:** 309–315.

Spealman R. D., Goldberg S. R. and Gardner M. L. (1981) Behavioral effects of nicotine: schedule-controlled responding in squirrel monkeys. *J. Pharmac. exp. Ther.* **216:** 484–491.

Valentine J. O. and Spealman R. D. (1983) Effects of caffeine and chlordiazepoxide on schedule-controlled responding of squirrel monkeys. *Fedn Proc. Fedn. Am. Socs exp. Biol.* **42:** 1158.

Wenger G. R. (1980) Cumulative dose–response curves in behavioral pharmacology. *Pharmac. Biochem. Behav.* **13:** 647–651.

Zuccarelli R. R. and Barrett J. E. (1980) A comparison of the effects of *d*-amphetamine, cocaine, imipramine, and pentobarbital on local and overall rates of responding maintained under a four-component multiple fixed-interval schedule. *Pharmac. Biochem. Behav.* **12:** 889–907.