Pharmacology Biochemistry & Behavior, Vol. 7, pp. 79–82.

Effects of Amphetamine and Methylphenidate on Fixed-Interval Responding in the Squirrel Monkey[1]

KATHERINE E. GOETHE[2] AND WALTER ISAAC[3]

University of Georgia, Athens, GA 30602

(Received 30 August 1976)

GOETHE, K. E. AND W. ISAAC. *Effects of amphetamine and methylphenidate on fixed-interval responding in the squirrel monkey*. PHARMAC. BIOCHEM. BEHAV. 7(1) 79–82, 1977. – The effects of oral doses of d-amphetamine and methylphenidate on a fixed-interval operant response were studied in four young male squirrel monkeys. A fixed-interval of 80 sec with a limited hold of 20 sec was used. Methylphenidate produced no observable changes in behavior, while d-amphetamine produced dose related changes in both the rate of responding and the temporal patterning of responses. Since dose levels used included, and exceeded, human clinical dosages, the present findings may have implications for future research involving the clinical use of these drugs.

Squirrel monkeys Operant d-Amphetamine Methylphenidate
Oral doses

COMPARATIVE studies of the effects of dextroamphetamine sulfate (Dexedrine) and methylphenidate hydrochloride (Ritalin), upon behaviors of non-human subjects are few. The effects of d-amphetamine and methylphenidate upon locomotor activity of the rat has been studied by Kallman and Isaac [3], who reported that methylphenidate increased locomotor activity in a manner similar to d-amphetamine, but was less potent on a milligram per kilogram basis. Both drugs interacted with ambient illumination levels and produced their greatest effects in the light, with a lesser effect in the dark.

Following an extensive review of the operant conditioning literature, Stretch and Dalrymple [8] concluded that in a wide variety of non-human subjects psychomotor stimulants such as d-amphetamine and methylphenidate increased response rates under schedules of reinforcement that lead to a low rate of responding while decreasing response rates under schedules of reinforcement that lead to a high rate of responding. That this effect may be a function of the reinforcement schedule, rather than response rate, was suggested by Stinnette and Isaac [7] who found on an FI 80 sec schedule that d-amphetamine decreased the response rate of the squirrel monkey in the dark, a low response rate condition, as well as in the light, a high response rate condition. They found, however, that this is not a characteristic of all stimulants, since caffeine increased the response rate in the light.

Using considerably longer intervals than Stinnette and Isaac [7], other investigators have observed an increase in response rates with d-amphetamine in squirrel monkeys on a fixed-interval task. McMillan [5], using a 5 min interval, and Kelleher and Morse [4], using a 10 min interval, observed rate increases at doses of less than 1.0 mg/kg; both studies reported a decrease in response rate at doses of 1.0 mg/kg.

The present study measured the effects of d-amphetamine and methylphenidate on operant behavior of squirrel monkeys on a fixed-interval schedule of reinforcement. On the basis of their clinical use in humans and their observed effects on rats, a similar effect on response rate in such a situation was to be expected.

METHOD

Animals

Four male squirrel monkeys (*Saimiri sciureus*) between one and two years old were used. The animals were housed in the colony room where a 12 hr light·12 hr dark schedule was maintained. The animals were fed a normal colony diet consisting of moistened Purina Monkey Chow, fresh vegetables, a vitamin supplement and ad lib water. Animals were fed at 6:00 a.m., tested in the afternoon, and fed about an hour after testing.

[1] This work was supported by a grant (MH 25164) from the National Institute of Mental Health.
[2] Present address: Department of Psychology, Virginia Commonwealth University, Richmond, VA.
[3] Requests for reprints should be addressed to Walter Isaac, Department of Psychology, University of Georgia, Athens, GA 30602.

Apparatus

An expanded-metal transport cage measuring 25 cm wide, 25 cm high, and 38 cm long served as the operant chamber. The cage ends were opaque Plexiglas modified to allow introduction of a 5 cm high and 1 cm diameter pedestal at one end through which reinforcements were delivered. A lever, 10 cm long and 2 cm wide, was mounted 8 cm above the floor, at the opposite end. Sweetened Hawaiian Punch was used as reinforcement. The pump delivering reinforcement produced an audible click when reinforcement was delivered.

The transport cage was centered in a white wooden enclosure 56 cm high, 41 cm wide and 44 cm long which was open at the top. The enclosure was centered in a sound attenuated cubicle 87 cm high, 92 cm wide and 54 cm deep that was open in the front. A fluorescent light mounted 77 cm from the floor of the cubicle provided an illumination level of approximately 55 ft-c (584.65 lx) at the floor of the apparatus.

Solid state programming equipment (BRS Digi-Bits), housed in another room, controlled the sequence of events and recorded responses and the number of reinforcements received by the animal.

Procedure

All animals were trained to press the lever to obtain reinforcement on a continuous reinforcement schedule and then shaped to an 80 sec fixed-interval schedule with reinforcement available for a maximum of an additional 20 sec. A cumulative summary of the number of responses made in each quarter of the 80 sec interval, as well as the number of reinforcements delivered, was obtained at the end of each session.

Drug administration began after a consistent fixed-interval pattern and rate of responding occurred on the reinforcement schedule. Six levels of d-amphetamine sulfate (placebo, 0.025, 0.05, 0.1, 0.2, 0.4 mg/kg) and six levels of methylphenidate hydrochloride (placebo, 0.05, 0.1, 0.2, 0.4, 0.8 mg/kg) were administered. (The d-amphetamine sulfate was generously provided by Smith, Kline and French Laboratories; the methylphenidate hydrochloride was generously provided by Ciba-Geigy Corporation.) All drug dosages were mixed with 5 cc of sweetened Hawaiian Punch and were administered orally. On placebo days animals were given 5 cc of sweetened Hawaiian Punch without drug. Animals were weighed every six days and drug doses were adjusted at those times.

Drug doses were assigned to each animal according to a sequence generated from a randomly selected six factor latin square. One replication required six days for the presentation of each drug dose and placebo, and a total of six replications under each drug was performed, for a total of 36 days. The first three replications were performed for adaptation to the drug and only the last three replications under each drug were analyzed. All animals received both drugs, but two received d-amphetamine first and two received methylphenidate first.

Upon completion of the total of the 12 replications, during which time all animals experienced a range of doses of both drugs, the effect of a combined dose of 0.2 mg/kg d-amphetamine and 0.4 mg/kg methylphenidate was administered to all animals for five consecutive days. Further, to evaluate the effects of a large dose of methylphenidate and any cumulative effects that might appear, the animals were given a daily dose of 3.2 mg/kg of the drug for five consecutive days.

Punch with the appropriate drug dosage was given each animal in the transport cage 15 min before being placed in the testing room. Each experimental session provided 30 opportunities for reinforcement and required about 40 min for completion.

RESULTS

The effect of each drug was evaluated separately by analysis of variance with the appropriate partitioning of error variance and degrees of freedom. Under both drug conditions the number of responses in the 20 sec quarters of the 80 sec interval differed significantly (d-amphetamine: $F(3,6) = 13.96$, $p < 0.01$; methylphenidate: $F(3,6) = 11.65$, $p < 0.01$). The fixed-interval pattern of responding, or scalloping, seen under the placebo conditions for both drugs was modified only by the d-amphetamine. A significant interaction between the dosage of d-amphetamine and the distribution of responses among the 20 sec quarter intervals was obtained, $F(15,30) = 7.79$, $p < 0.01$. The effect of d-amphetamine upon the total number of responses was also significant, $F(5,10) = 6.13$, $p < 0.01$. As shown in Fig. 1, doses of 0.1, 0.2, and 0.4 mg/kg of d-amphetamine decreased response rates under the 80 sec fixed interval schedule and altered the temporal patterning of responses as well. Methylphenidate, however, did not alter the total number of responses made or influence the temporal patterning of those responses (Fig. 2).

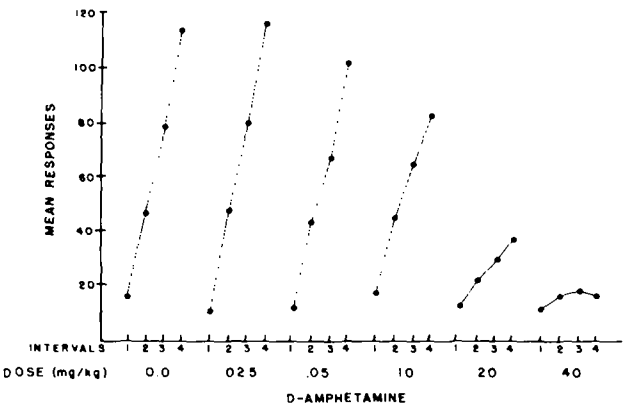

FIG. 1. The distribution of responses among the four 20 sec quarters of the 80 sec interval for each of the oral d-amphetamine doses.

Whether the animals had experienced d-amphetamine or methylphenidate as the first or second drug produced no significant effect on any measure. Further, the animals showed normal gains in body weight under both drugs.

The combined dose of 0.2 mg/kg d-amphetamine and 0.4 mg/kg methylphenidate did not produce a change in response frequency over the five days that it was administered. When the mean scores for the five days with the combined dose were compared to the mean scores of the separate doses of 0.2 mg/kg d-amphetamine and 0.4 mg/kg

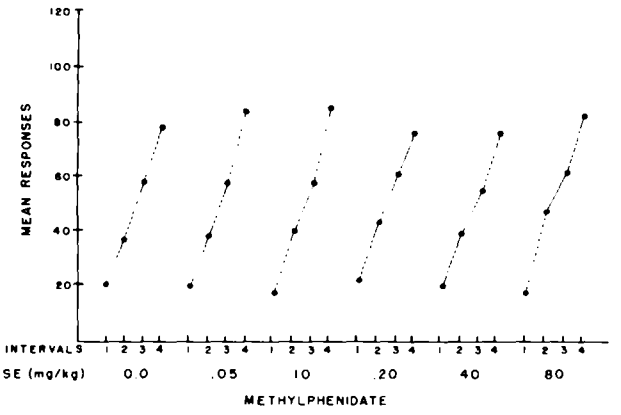

FIG. 2. The distribution of responses among the four 20 sec quarters of the 80 sec interval for each of the oral methylphenidate doses.

methylphenidate the drug effect was found not significant at the 5% level.

Similarly, when the effect of the large dose, 3.2 mg/kg, of methylphenidate was evaluated, no significant difference was found over the five day period that it was administered. When a comparison was made of the mean scores for the five day period with the mean scores made under the placebo conditions the decrease in response rates was found not to be significant at the 5% level.

The absence of differences in response rates over orders, or days, of drug administration argue against the development of tolerance to the drugs.

DISCUSSION

D-amphetamine and methylphenidate do not produce the same effects in squirrel monkeys as they do in rats where d-amphetamine and methylphenidate appear to have stimulant effects. The results of Stinnette and Isaac [7] were replicated and the conclusion that d-amphetamine reduces the response rate on an 80 sec fixed-interval schedule was verified; no stimulant effect was observed at even low dose levels. The effect of d-amphetamine upon the squirrel monkey over a wide range of dose levels was that of a depressant.

Methylphenidate, having similar effects in rats to d-amphetamine [3], had no effect upon the fixed-interval task studied. Thus, unlike caffeine which produces an increase in responding and d-amphetamine which produced a decrease in responding [7], methylphenidate had no effect upon responding. Methylphenidate, unlike d-amphetamine which altered not only the rate of responding but also the temporal pattern of responses, had no effect upon either aspect of the behavior. Considering their similar effect upon locomotor activity in the rat and their similar clinical effect in humans at comparable doses, these findings were surprising.

Other investigators have examined the effects of d-amphetamine upon performance on a fixed-interval task by the squirrel monkey. Using intervals of five min [5], and 10 min [4], an increase in response rates at low doses of the drug has been observed. Because of the small number of measures obtained on small samples of food deprived animals, along with no statistical evaluation of the effects obtained, it is difficult to integrate their work with the present findings. Further, a lack of adaptation to injection procedures and altered physiology produced by the drugs confounds their findings.

Dextroamphetamine sulfate and methylphenidate hydrochloride are reported to be similar in their effect of reducing hyperactivity in children [2,9]. While methylphenidate has been reported to be the most popular drug in the treatment of hyperactivity, there is disagreement as to the relative efficacy of the two drugs. Regardless of preferences between the drugs, they are consistently listed as the most effective or second most effective drugs in the treatment of hyperkinesis [1,2].

An attempt was made to include a range of doses for both drugs that might be of clinical usefulness. A survey of several sources suggested that a dose of 15 mg is a reasonable dose of both drugs for the human. Transforming this dose to an equivalent dose for the squirrel monkey would indicate that a dose of approximately 0.1 mg is appropriate if body weight is used in the calculation of dosage. If body surface area is used in the calculation, about 0.3 mg is appropriate. The dose range used in the present study encompasses both values of both drugs. Since there are suggestions in the literature that total daily doses of up to 60 mg of methylphenidate may be used clinically [6] a single high dose equivalent to almost twice this value was included. Oral doses of d-amphetamine within a dose range of that used clinically produced a decrease in the response rate of the squirrel monkey. Oral doses of methylphenidate, on the other hand, produced no significant effect even at very high doses.

The present study would suggest that generalizations concerning the stimulant effect of drugs across phylogenetic levels is hazardous. Further, if the effects of these drugs upon the squirrel monkey are more similar to the effect of these drugs on humans than are the effects of these drugs on rats when generalized to humans, the present findings may also have implications for further human investigations.

REFERENCES

1. Eveloff, H. H. Radiatric Psychopharmacology. In: *Principles of Psychopharmacology*, edited by W. Clar and J. Guidice. New York: Academic Press, 1970, p. 694.
2. Fischer, K. C. and W. P. Wilson. Methylphenidate and the hyperkinetic state. *Dis. nerv. Syst.* **32:** 695–698, 1971.
3. Kallman, W. M. and W. Isaac. The effects of age and illumination on the dose-response curves for three stimulants. *Psychopharmacologia* **40:** 313–318, 1975.
4. Kelleher, R. T. and W. H. Morse. Escape behavior and punished behavior. *Fedn Proc.* **23:** 808–817, 1964.
5. McMillan, D. E. Some interactions between sympathomimetic amines and amine-depleting agents on the schedule-controlled behavior of the pigeon and the squirrel monkey. *J. Pharmac. exp. Ther.* **163:** 172–187, 1968.
6. Medical Economics, Inc. *Physicians' Desk Reference.* New Jersey: Litton Publications, 1976, p. 724.

7. Stinnette, M. J. and W. Isaac. Behavioral effects of d-amphetamine and caffeine in the squirrel monkey. *Eur. J. Pharmac.* 30: 268–271, 1975.
8. Stretch, R. and D. Dalrymple. Effects of methylphenidate, pentobarbitol, and reserpine on behavior controlled by a schedule of inter-response time reinforcement. *Psychopharmacologia* 13: 49–64, 1968.
9. Werry, J. and R. Sprague. Hyperactivity. In: *Symptoms of Psychopathology*, edited by C. Costello. New York: Wiley, 1970, pp. 397–417.