Pharmacology Biochemistry & Behavior, Vol. 29, pp. 281–285. © Pergamon Press plc, 1988. Printed in the U.S.A. 0091-3057/88 $3.00 + .00

Variability in the Effects of 4-Bromo-2,5-Dimethoxyamphetamine (DOB) on Operant Behavior of Squirrel Monkeys

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Received 10 July 1987

McKEARNEY, J. W. *Variability in the effects of 4-bromo-2,5-dimethoxyamphetamine (DOB) on operant behavior of squirrel monkeys.* PHARMACOL BIOCHEM BEHAV **29**(2) 281–285, 1988.—Effects of the hallucinogenic drug (+/−)-4-bromo-2,5-dimethoxyamphetamine HCl (DOB, 0.003–0.3 mg/kg) were studied in squirrel monkeys. Only decreases in responding were seen in monkeys studied under 5-min fixed-interval schedules of food presentation. These decreases were blocked by pretreatment with the 5-HT_2 antagonist ketanserin (0.1–1.0 mg/kg) and by the non-selective 5-HT antagonists methysergide (0.3 mg/kg) or mianserin (0.1–1.0 mg/kg). Similar decreases in responding and antagonism by 5-HT antagonists were seen at slightly higher doses of DOM HCl (methyl rather than bromo at the 4 position). In contrast to effects under the food schedule, DOB initially produced marked increases in responding of three monkeys studied under schedules of shock avoidance. However, a complex pattern of changes in the effects of DOB emerged when the same doses were given on subsequent occasions. In one monkey, there were graded increases in responding to a peak of just over 200% of control at 0.17 mg/kg when DOB was given in a roughly ascending dose series. However, no increases in responding were observed at any dose when DOB was given on many subsequent occasions (some very widely spaced). A second monkey showed similar increases initially, but responding was suppressed by a formerly rate-increasing dose of DOB (0.1 mg/kg) on two subsequent test days. Later, this dose again produced increases in responding of about the same magnitude as seen initially, but these increases eventually diminished and were no longer observed. In the third monkey, increases in responding after the initial ascending dose series diminished in an irregular manner over the course of successive redeterminations.

4-Bromo-2,5-dimethoxyamphetamine (DOB) 4-Methyl-2,5-dimethoxyamphetamine (DOM) Ketanserin
Serotonin antagonists Squirrel monkeys Operant behavior

A number of phenylisopropylamine compounds are potent hallucinogens in man, and readily substitute for drugs such as LSD in animals studied under drug-discrimination procedures [6, 7, 13]. Compounds with 2,5-dimethoxy substitution seem to be particularly potent in this regard, and the same drugs display a great deal of selectivity for the 5-HT_2 as opposed to the 5-HT_1 receptor subtype in ligand binding studies [5,12]. These compounds include several 2,5-dimethoxy-4-*X*-amphetamines, where *X*=methyl (DOM), bromo (DOB), or iodo (DOI). Behavioral and neurochemical evidence shows that the (−)-isomers of these compounds are more potent than the racemate or the (+)-isomers [1, 3, 4]. Inasmuch as DOM, DOB, and DOI readily substitute for one another in drug discrimination experiments (e.g., [7]), it is probable that their primary mechanism of action is common.

Ongoing research in this laboratory is focusing on characterization of the behavioral effects of drugs active at the putative 5-HT_1 and 5-HT_2 receptor subtypes. Because DOB displays about a 50-fold greater affinity for 5-HT_2 as opposed to 5-HT_1 binding sites [5], we were interested in comparing its behavioral effects with those of other 5-HT agonists. Apart from a number of drug discrimination experiments, the behavioral effects of DOB appear not to have been studied widely. DOB was reported to have effects similar to those of LSD on rat locomotor activity in the open field [1]. In addition, there is one report that low doses of DOB increased responding and higher doses decreased responding of rats performing under a shock avoidance schedule [3].

In the experiments to be summarized here, the effects of (+/−)-DOB HCl were studied in squirrel monkeys responding under fixed-interval schedules of either food presentation or termination of stimuli associated with impending electric shock delivery, or under continuous shock-avoidance schedules. The effects of pretreatment with several 5-HT antagonists were also studied. Limited observations on the effects of (+/−)-DOM HCl were done in the same monkeys.

METHOD

Subjects and Apparatus

Four adult male, and one adult female (S-583), squirrel monkeys were used. All had extensive experience with administration of drugs and with various schedules of reinforcement. Monkeys studied under food delivery schedules

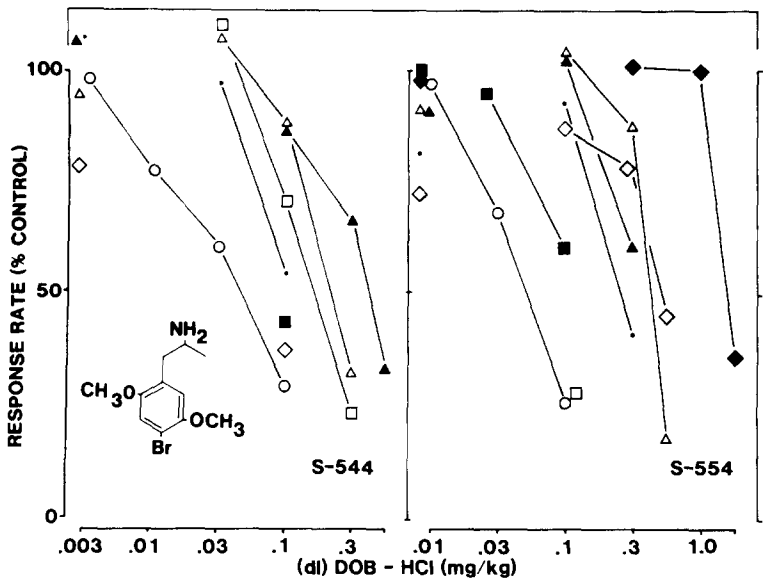

FIG. 1. Effects of DOB on responding under the FI schedule of food presentation in two monkeys. The chemical structure of DOB is shown in the left panel. Open circles: DOB alone. Symbols for combinations of DOB with antagonists are as follows. Large filled symbols: mianserin; unfilled symbols: ketanserin (squares=0.1, triangles=0.3, and diamonds=1.0 mg/kg). Small dots: 0.3 mg/kg methysergide. Open symbols at the extreme left of each panel show the effects of antagonists given alone. In general, points are means of at least two determinations.

were maintained at 80% of free-feeding body weights, but others had unlimited access to food and water in the living cages.

Experiments were conducted with monkeys seated in a Plexiglas chair. Where appropriate, electric shocks were delivered through metal electrodes that rested on a shaved portion of the tail. Shock intensity was 7 mA for monkey S-583 and 10 mA for S-525 and S-574 (650 V AC, about 200 msec in duration). For all monkeys, a response key (BRS/LVE, No. 121-05 or Coulbourn No. E21-03) requiring about 15 g force for operation was mounted on a clear panel facing the monkey. Three pairs of 7-W colored lights were mounted behind this panel. For monkeys S-544 and S-554, food pellets (300 mg, Noyes formula L) were delivered to a receptacle mounted on the same panel at waist level. Chairs were housed in ventilated, sound-attenuating chambers in a room distant from programming and recording equipment.

Procedures

Monkeys S-544 and S-554 responded under a 5-min fixed-interval (FI) schedule of food presentation; that is, the first response after each 5-min period had elapsed resulted in the delivery of a food pellet. The procedure for S-554 differed slightly in that the 5-min FI alternated with a schedule in which each 30th response resulted in food delivery (for the most part, only results from FI components are presented here). Experimental sessions ended with the completion of either 10 (S-554) or 20 (S-544) FI cycles.

Monkey S-583 responded under a 5-min FI schedule of stimulus-shock termination. When the chamber lights were lit, shocks were scheduled to be delivered every 5 sec after the 5-min FI had elapsed, but a single response after 5 min extinguished the lights for 30 sec and precluded delivery of shock. FI components alternated with a schedule in which 30 responses were required to prevent shock; as with monkey S-554, only results from FI components are presented here. Sessions terminated after completion of 15 FI cycles.

Monkeys S-525 and S-574 responded under a continuous shock-postponement schedule. In the absence of responding, shocks were scheduled for delivery every 30 sec but each response postponed shock delivery for 30 sec. Four 15-min periods under this schedule were separated by 5-min periods of darkness in which no schedule was in effect.

It should be noted that certain differences in schedule conditions for the various monkeys (e.g., session durations, multiple- vs. single-component schedules, type of avoidance schedule, shock intensity) were not deliberate experimental variables for purposes of the experiments reported. Rather, the monkeys available for use at the beginning of these experiments already had considerable experience under their respective experimental procedures. That the results to be reported differed among monkeys only according to whether responding was maintained by food delivery as opposed to shock avoidance indicates that this was the primary determinant of differences in drug effects and that the other differences in procedural detail had no detectable influence.

Drugs

(+/−)-4-Bromo-2,5-dimethoxyamphetamine HCl (DOB) and (+/−)-4-methyl-2,5-dimethoxyamphetamine HCl (DOM) were furnished by the National Institute on Drug Abuse. Ketanserin tartrate was generously supplied by Janssen Pharmaceutica (Beerse, Belgium), methysergide maleate by Sandoz Pharmaceuticals (E. Hanover, NJ), and

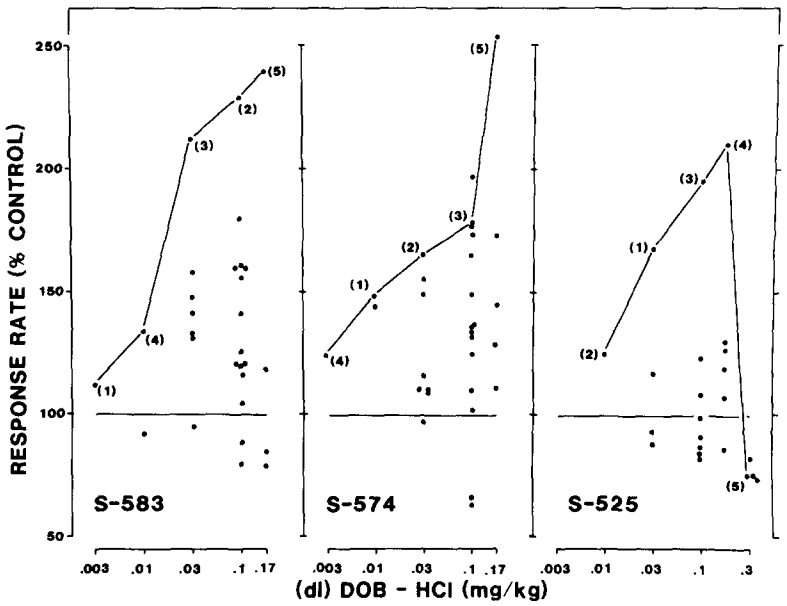

FIG. 2. Effects of DOB on responding under the schedule of stimulus-shock termination (S-583) or of shock postponement (S-574 and S-525). Connected points are for the first determination of the effects of each dose. Numbers in parentheses represent the order in which each dose was first given. Unconnected points are from subsequent experimental sessions. All points are from single experimental sessions.

mianserin HCl by Organon (Oss, Holland). All were dissolved in sterile distilled water. Injection volume was usually 0.5 ml/kg, given in the thigh muscle. DOB or DOM were injected just before sessions. When given, ketanserin, mianserin, or methysergide were given 15 min prior to DOB or DOM. Experimental sessions were conducted 5 days weekly. Drugs were generally given on Tuesdays and Fridays, and performance on Thursdays was averaged to compute estimates of control responding.

RESULTS

The pattern of responding under the FI schedules of food presentation and of stimulus-shock termination was characteristic of that seen under this schedule; a period of little or no responding was followed by an increasing response rate until the FI terminated. Under the shock-postponement schedule, there was a steady moderate rate of responding, and few shocks were delivered.

Food Presentation Schedules

DOB decreased responding under the FI schedule of food delivery (Fig. 1). At the highest dose studied alone (0.1 mg/kg), responding was suppressed to about 30% of control in S-544 and was virtually completely suppressed in S-554. It should be noted that these decreases in fixed-interval responding were graded in nature, and not the result of extended periods of no responding (cf., later description of DOM effects). For example, for monkey S-544, the duration of experimental sessions changed no more than 1% at any of the DOB doses shown in Fig. 1.

Pretreatment with 0.3 mg/kg ketanserin resulted in a rightward shift in the DOB dose-effect curve. This dose of ketanserin was ineffective when given alone. A lower dose of ketanserin (0.1 mg/kg) was about as active in blocking DOB effects in monkey S-544, but appeared not to have appreciable effects in the other monkey. A dose of 1.0 mg/kg ketanserin itself decreased responding. This dose was effective in antagonizing DOB effects only in monkey S-554. Methysergide (0.3 mg/kg) and mianserin (0.1–1.0 mg/kg) also shifted the DOB dose-effect curve.

Shock Schedules

When given in approximately ascending order up to 0.17 mg/kg, DOB markedly increased responding in all three monkeys (connected points, Fig. 2; order of administration indicated by numbers next to data points). When the same doses were given on later occasions, however, the effects differed both qualitatively and quantitatively (unconnected points, Fig. 2).

Figure 3 shows the effects of 0.03 mg/kg (open, unconnected circles), 0.1 mg/kg (filled, connected circles), and 0.17 mg/kg DOB (unconnected diamonds) in monkey S-574 on a number of different occasions (note that days refer to real time rather than to test sessions, and that the effects of 0.003 and 0.01 mg/kg are not plotted here). These results are difficult to characterize except to say that, in general, there was a diminution in the rate-increasing effects over time. Control rates of responding did not differ appreciably over the course of time during which these effects were determined. The rate increases seen with 0.1 mg/kg did seem to be blocked by pretreatment with 0.3 mg/kg ketanserin (filled triangles), but this must be interpreted with caution due to the variability in the effects of DOB itself. The same general pattern of diminution in rate increasing effects was also seen with the other two monkeys (data not shown).

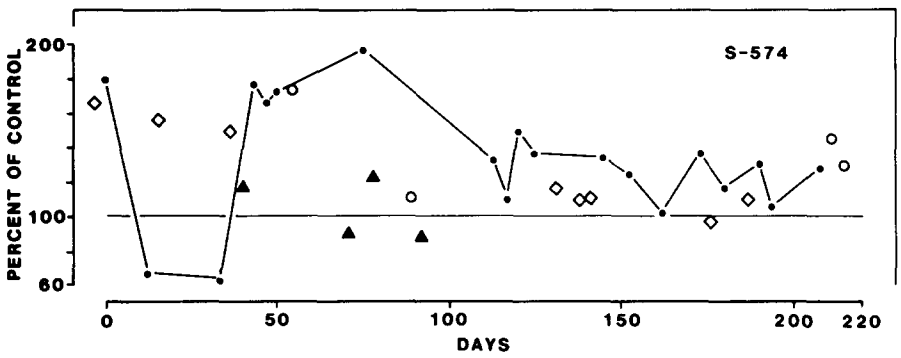

FIG. 3. Multiple determinations of the effects of DOB (monkey S-574). Data points are from the center panel of Fig. 2. Diamonds: 0.03 mg/kg. Connected points: 0.1 mg/kg. Open circles: 0.17 mg/kg. Filled triangles show the effects of 0.1 mg/kg DOB in combination with 0.3 mg/kg ketanserin. Note that the plot is across successive real days (rather than test sessions). Day zero is the first occasion on which 0.1 mg/kg (the most frequently studied dose) was given.

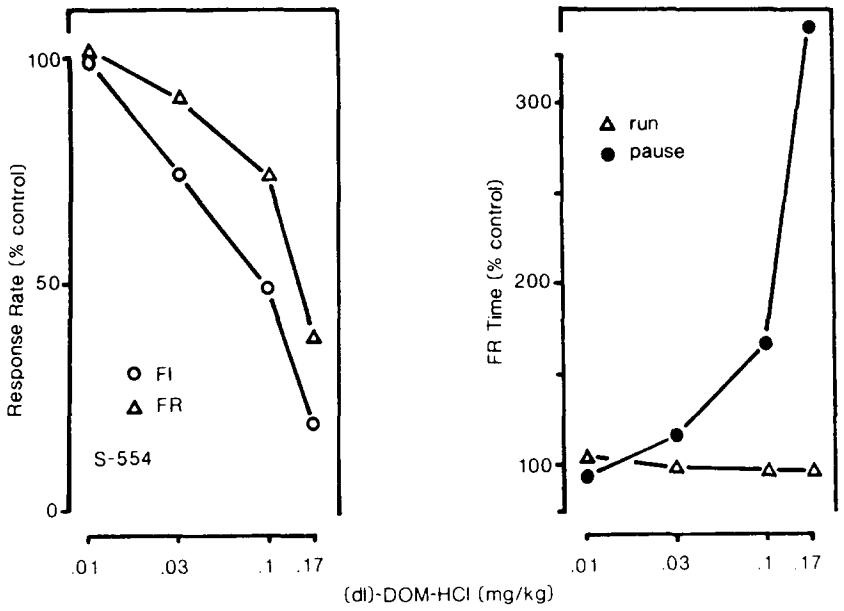

FIG. 4. Effects of DOM on FI and FR responding (monkey S-554). Left panel: overall rates of responding (responses/sec, expressed as % control). Right panel: time before initiation of FR sequence (pause) and time to complete FR once initiated (run), both expressed as % control. Overall control response rates were about 0.25 responses/sec for FI and 2.0 per sec for FR. Average control pause time was about 9 sec per FR, and run time was about 5 sec per FR (equalling a local rate of about 6 responses/sec). Although there was a 90-sec limit for completion of each 30-response FR sequence, increased pausing rarely resulted in expiration of the time limit (on one of the two occasions when the highest dose was given, 2 of the 10 reinforcers available under the FR schedule was not obtained). Data points are means of at least two determinations.

Effects of DOM

As with DOB, DOM (0.01–0.3 mg/kg) decreased responding in the monkeys studied under the food presentation schedule. DOB was roughly 2–3 times more potent than DOM in decreasing responding. Figure 4 illustrates the effects of DOM in the monkey studied under the multiple fixed-interval (FI) fixed-ratio (FR) schedule of food delivery. Overall rates of FI responding were decreased to a somewhat greater extent than FR responding (left panel). As with the effects of DOB under this schedule, the DOM effects on FI responding were due to overall decreases in responding rather than to periods of no responding. The decreases in FR responding, however, were due to increases in the pause occurring prior to execution of each response sequence (right panel). In all particulars, the effects of DOM illustrated in Fig. 4 were the same as those seen with DOB (except that DOB was slightly more potent).

The DOM dose-effect curve was shifted to about the same extent as seen with DOB when animals were pretreated with various doses of ketanserin, mianserin, or methysergide

(data not shown). The effects of DOM in the monkeys studied under the shock schedules were, unfortunately, studied only after the monkeys had ceased showing rate increases with DOB. No increases in responding were observed over the dose range studied (0.03–1.0 mg/kg).

DISCUSSION

DOB and DOM decreased responding maintained by food delivery under FI or multiple FI FR schedules. While the decreases in FI were due to an overall lessening of responding, the effects under the FR schedule were due entirely to increases in the duration of pausing before response initiation. A related effect of a number of hallucinogenic drugs on response pausing in rats studied under FR schedules has been reported many times (for review see [11]). Decreases in food-maintained responding produced by DOB (and by DOM) were blocked by the selective 5-HT_2 anatagonist ketanserin and by the non-selective 5-HT antagonists mianserin and methysergide, suggesting that this behavioral effect is mediated via a 5-HT_2 action. In rats, decreases in food-maintained responding produced by DOM [10] as well as the discriminative-stimulus properties of DOM [8], have also been reported to be blocked by selective 5-HT_2 antagonists. The relative potency difference between DOB and DOM in the present experiments (about 2- to 3-fold) is about the same as that reported for the discriminative-stimulus properties of these drugs, and for their relative affinities for 5-HT_2 binding sites (e.g., [7]).

The extreme variability in results obtained with DOB in the monkeys studied under the shock schedules has no ready explanation. Qualitative differences in the effects of DOB under the food and shock schedules are noteworthy but not without precedent, since a number of drugs have effects that differ depending on the type of event controlling behavior (e.g., [2,9]). However, it is not clear why the rate increases should be subject to so much variability (whereas rate decreases under the food schedule were reliably seen). Unfortunately, excess variability in the effects of DOB under the shock schedule precluded determination of the likely mechanism responsible for the response rate increases. Limited tests with ketanserin in one monkey suggest the possibility that 5-HT_2 actions may be involved, but variability in the effects of DOB itself clouds any such interpretation. Although it is difficult to be certain, it is unlikely that the rate increases were in any way like those produced by amphetamine (i.e., DOB minus the aromatic substituents), since amphetamine produces increases in responding under conditions similar to those of the present experiment (e.g., [9]) without regard to whether behavior is controlled by food or by shock.

ACKNOWLEDGEMENTS

This work was supported by grants DA-01015 and MH-18421 from the USPHS. I thank Janssen Pharmaceutica, Sandoz Pharmaceuticals, and Organon for gratis samples of drugs, and J. B. Smith for comments on an earlier form of the manuscript.

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