*Pharmacology Biochemistry & Behavior*, Vol. 7, pp. 307–310. 

# Stereoselective Effects of 1-(2,5-Dimethoxy-4-Methylphenyl)-2-Aminopropane (DOM) on Schedule-Controlled Behavior[1]

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(Received 9 May 1977)

HARRIS, R. A., D. SNELL AND H. H. LOH. *Stereoselective effects of 1-(2,5-dimethoxy-4-methylphenyl)-22-aminopropane (DOM) on schedule-controlled behavior.* PHARMAC. BIOCHEM. BEHAV. 7(4) 307–310, 1977. – The effects of R(−)-, S(+) and R, S-1-2-5-dimethoxy-4-methylphenyl)-2-Aminopropane (DOM) were studied using rats responding under a fixed interval two-min schedule of food presentation. All three drugs decreased average rates of responding in a dose-related manner, with R-DOM being five to six times more potent than S-DOM but only about 1.2 times more potent than R,S-DOM. Relatively high doses of R,S-DOM and S-DOM increased the low response rates occurring at the beginning of the fixed interval and decreased the higher response rates occurring at the end of the interval (rate-dependent effects). These results are discussed in terms of the stereoselective metabolism of DOM and of the structural similarities between R-DOM and the behaviorally active isomer of LSD.

DOM isomers Schedule-controlled behavior Rate-dependence

STUDIES of the structural requirements for hallucinogenesis have shown that small changes in the structure or configuration of hallucinogenic drugs may drastically alter their behavioral effects [18]. For example, the (+) isomer of LSD with the configuration (5–R; 8–R) (Fig. 1) is much more active in humans than is either (−) LSD (5–S; 8–R) or (−) isoLSD (5–S; 8–S) [17,21]. Regarding the hallucinogenic derivatives of 1-phenyl-2-aminopropane (amphetamine), the R(−) isomer of 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (2,5-dimethoxy-4-methylamphetamine, DOM, STP) is considerably more potent than the S(+) isomer in producing hallucinogenic effects in humans [19] and in altering avoidance behavior in rats [4] and body temperature in rats and rabbits [1,2]. We have recently tested the effects of a number of hallucinogens using schedule-controlled behavior and have noted that the potency of these drugs in reducing responding under a fixed interval two minute (FI–2) schedule of food presentation is correlated with their potency for producing subjective effects in humans [10,11]. In view of this correlation, it was of interest to extend this comparison using stereoisomers with known human potencies. Thus, the effects of various doses of the R– and S-isomers of DOM were evaluated in the present study using a FI–2 schedule. In addition, the racemate was also studied as it has recently been noted that an enantiomeric interaction may allow inhibition of the metabolism of the R-isomer by the S-isomer [14, 15, 23, 24]. Thus, if the behavioral effects of R–DOM are altered by metabolism, the effects of the racemate would not be accurately predicted from the effects of the individual isomers. Although a number of drugs are known to be stereoselectively metabolized [8,15], the behavioral consequences of this selective metabolism have received only limited attention [16]. In this communication we propose that the potency of R,S–DOM in altering schedule-controlled responding reflects stereoselective metabolism.

## METHOD

### *Animals*

Three male Sprague-Dawley rats obtained from Simonsen Laboratories, Gilroy, CA and weighing between 400 and 450 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 previously been used in studies involving hallucinogens [11] but had not been administered any drug for about two weeks before beginning these experiments.

### *Apparatus*

Standard rat test cages (Grason-Stadler, West Concord, MA) 23 cm long, 29 cm wide and 19 cm high were installed in sound attenuating chambers (Grason-Stadler, West

[1] This work was supported by Public Health Service Grants MH–25487 and DA–02785.
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Concord, MA). The manipulandum consisted of a cylindrical lever 0.6 cm in diameter and 2.5 cm long (BRS/LVE, Beltsville, MD) and movement of the lever (about 30 g force required at the tip) in a vertical or lateral direction was 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*

The animals responded under a fixed interval 2 min (FI–2) schedule of food presentation [7], where the first response after two min had elapsed produced two 45 mg food pellets (P. J. Noyes Co., Lancaster, NH). The cumulative responses within each 20 sec segment of the fixed interval were recorded by digital counters. The sessions were terminated after presentation of 24 fixed intervals or fifty min, whichever occurred first. Animals were tested Monday through Friday of each week.

*Drugs*

The following drugs were used: S(+)-amphetamine sulfate (Sigma Chemical Co., St. Louis, MO) and S(+)-, R(−)- and R,S-1-(2,5-dimethoxyl-4-methylphenyl)-2-aminoproprane HCL (DOM), kindly supplied by Dr. Neal Castagnoli, Jr., Department of Pharmaceutical Chemistry, University of California, San Francisco, CA. Various doses of the drugs (dosage as the salt, dissolved in 0.9% NaCl, 1 ml/kg = injection volume) were injected 5 min before the beginning of the session. S-amphetamine was administered by the subcutaneous (SC) route, and the other drugs were injected intraperitoneally (IP). Each dosage was administered twice to each of the three animals, and drug injection were separated by at least 72 hr. Drugs were given in an ascending-descending dose order in the following sequence: S-amphetamine, R,S–DOM, S–DOM, R–DOM. For each drug, similar effects were observed during the ascending and descending dose orders, indicating that tolerance did not develop to the drug effects.

*Measurement of Drug Effects*

The average control response rates for evaluating the effects from the drug injections were calculated from six to eight non-treatment days occurring before and after each series of drug injections. Responding during sessions conducted on Thursdays was also used to calculate control rates. Drugs were injected on Tuesdays and Fridays. The response 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 [6] and others [11,12]. The data for each animal was fitted to a straight line by the method of least squares. The potency ratio and 95% confidence limits were determined for R– and R,S–DOM (using dosages of 0.3 to 1.0 mg/kg) by the parallel line analysis of graded responses as described by Goldstein [9].

## RESULTS

*Effects of R–, S– and R,S–DOM on Average Rates of Responding*

As is shown in Fig. 2, both isomers of DOM as well as the racemate decreased the average rates of responding under the FI–2 schedule in a dose-related manner. However, the R-isomer and the racemate were much more potent in this respect than was the S-isomer. Doses of R–DOM as low as 0.3 mg/kg were found to reduce responding, whereas a dose of 3.0 mg/kg of S–DOM was required to produce a marked reduction of responding. The dose of each drug required to reduce responding to 50% of control rates ($ED_{50}$), as estimated from the data in Fig. 2, was 0.47 mg/kg for R–DOM, 0.61 mg/kg for R,S–DOM and 2.7 mg/kg for S–DOM. Thus, the R-isomer was almost 6 times more potent than the S-isomer. The potency ratio and 95% confidence limits for R– and R,S–DOM was 1.22 (0.48 to 1.96), indicating that the racemate was more potent than would be predicted based on the potencies of the individual isomers.

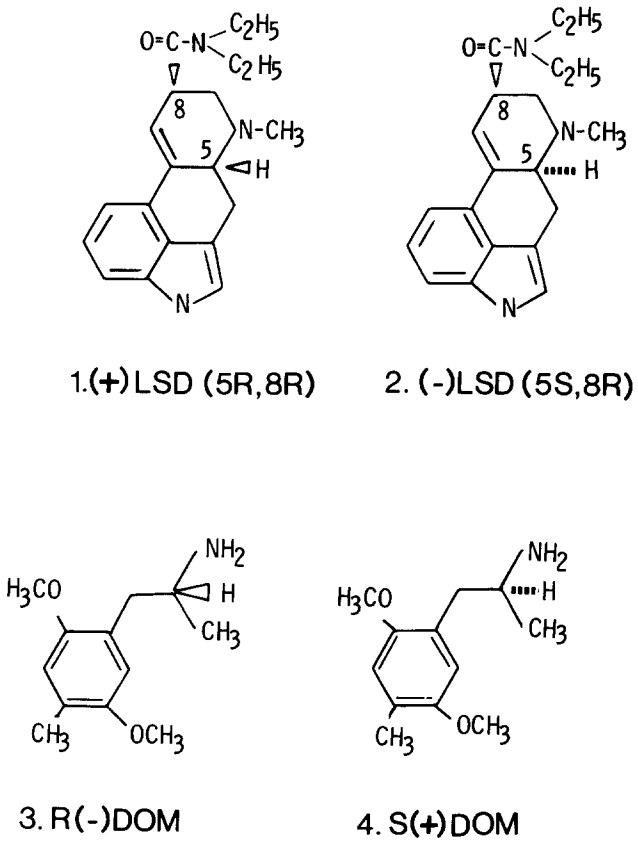


FIG. 1. Chemical structures of the stereoisomers of LSD and DOM.

*Effects of S-Amphetamine, R–, S– and R,S–DOM on Local Rates of Responding*

Under the FI–2 schedule of food presentation, there were low rates of responding (0.001 to 0.01 res/sec) at the beginning of each interval, increasing rates of responding throughout the interval, and high rates of responding (1 to 3 res/sec) at the end of each interval. Some of the drug treatments increased the low rates of responding occurring at the beginning of the intervals while decreasing the high rates of responding occurring at the end of the intervals. These types of effects have been termed rate-dependent by

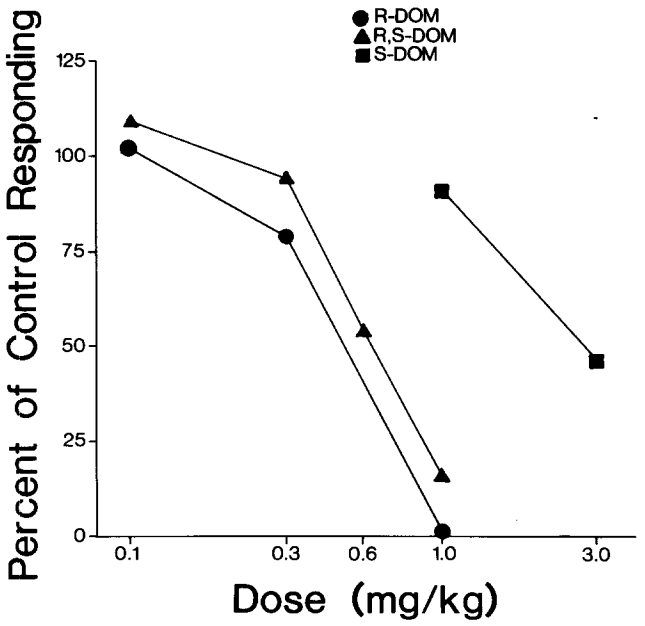


FIG. 2. Effects of R(−)-, S(+)- and R,S-DOM on average rates of responding under a fixed-interval two minute schedule of food presentation. Drug effects are given as a percent of the control rates of responding; the control rate (mean ± SEM for 8 determinations in each of 3 rats) was 0.44 ± 0.01 responses/second.

TABLE 1

DRUG EFFECTS EVALUATED AS A FUNCTION OF THE CONTROL RATE OF RESPONDING

| Drug | Dose (mg/kg) | Slope | Y as % of X when X = 1 res/sec | Correlation Coefficient |
|---|---|---|---|---|
| R,S-DOM | 0.1 | −7° | 85 | 0.75 |
| | 0.3 | 0.4° | 96 | 0.20 |
| | 0.6 | −8° | 46 | 0.93 |
| | 1.0 | −29° | 12 | 0.96 |
| R(−)-DOM | 0.1 | 3° | 100 | 0.33 |
| | 0.3 | −3° | 72 | 0.67 |
| | 1.0 | | No Responding | |
| S(+)-DOM | 1.0 | 5° | 91 | 0.76 |
| | 3.0 | −18° | 34 | 0.81 |
| S(+)-amphetamine | 1.0 | −29° | 51 | 0.97 |

Shown here are the average slopes and correlation coefficients (r) of the regression lines and average response rates after drug injection as % of control when the control rate is one response per second. Data are means derived from duplicate determinations in three animals.

Kelleher and Morse [12]. The present rate-dependent effect may be summarized and compared on the basis of the slopes, intercepts and correlation coefficients of regression lines fitted to a plot of log control response rate vs. drug effect, where the drug effect is given as log percent of control responding [6, 12, 13]. These data are presented in Table 1. It can be seen that a dose of 1.0 mg/kg R,S–DOM produced rate-dependent effects as judged by the marked negative slope (−29°) of the regression line. However, this pronounced rate dependence was observed only with a dose of R,S–DOM which greatly suppressed the overall rate of responding (Fig. 2). R–DOM did not produce rate-dependent effects at any dosage tested; however, a limited supply of this isomer prevented testing of a dose which would markedly, but not completely, reduce the overall rate of responding. A dose of S–DOM (3 mg/kg) which reduced the average response rate by about 50% produced rate dependent effects, as judged by a slope of −18° (Table 1). In contrast, a dose of R,S–DOM (0.6 mg/kg) which similarly reduced average rates of responding, produced little, if any, rate-dependency (slope = −8°). For comparison, a dose of S-amphetamine (1 mg/kg) which reduced average rates of responding by about 50% also produced marked rate-dependent effects (slope = −29°).

## DISCUSSION

The R(−) isomer of DOM was found to be about 5 to 6 times more potent than the S(+) isomer in reducing the average rate of responding maintained by an FI–2 schedule. This is in agreement with reports that the R-isomer is at least 4 times more potent than the S-isomer in producing subjective effects in humans [19], and in altering avoidance behavior in rats [4] and colonic temperature in rabbits and rats [1,2].

Considering the low activity of the S-isomer found in this study, the racemic mixture would be expected to be about half as potent as the R-isomer. However, the racemate was found to be only slightly less potent than the R-isomer in decreasing the average rate of responding. This unexpectedly high potency of the racemate may be related to the apparent retardation of the metabolism of R–DOM in the presence of S–DOM [14,15]. This preferential metabolism of the S-isomer component of the racemic mixture results in a decreased metabolism of the R-isomer which may lead to higher brain levels of the active isomer after injection of the racemate than after injection of the R-isomer alone [15]. This suggests that the metabolism of hallucinogenic 1-phenyl-2-aminopropanes may alter their behavioral effects even if these effects are measured shortly after administration of the drug (5 to 50 min as in the present experiments).

The individual isomers of DOM and the racemate also differed in their tendency to increase the low rates of responding occurring at the beginning of the interval while decreasing the high rates of responding at the end of the interval (rate-dependent effects). The rate-dependent effects, which were most pronounced for the racemic mixture, were also produced by the S-isomer. Rate-dependent effects of the racemate were also noted by Tilson *et al.* [22]. It is not clear from these studies if the R-isomer produces rate-dependent effects or if some interaction between the R– and S-isomers occurs to produce the rate-dependent effects observed with the racemate. Interestingly, it has been reported that the effects of racemic 1-(3,4-dimethoxyphenyl)-2-aminopropane (3,4-dimethoxyamphetamine) on avoidance behavior cannot be produced by administration of either of the individual isomers [2]. The possibility that these

differences may be related to stereoselective metabolism and production of behaviorally active metabolites is currently under investigation in this laboratory.

It is of interest to compare the effects of R– and S–DOM to the effects obtained with R- and S-amphetamine using the same FI–2 min schedule ([10,20] and Harris, unpublished results). Addition of the 2,5-dimethoxy and 4-methyl substituents to amphetamine differentially affected the two isomers as the potency of R–DOM is greater than that of R-amphetamine (l-amphetamine), while the potency of S–DOM is less than that of S-amphetamine (d-amphetamine). Also the marked rate-dependency produced by S-amphetamine is much less pronounced with S–DOM. As the effects of R,S–DOM on fixed ratio responding are decreased by cinanserin, a serotonin receptor blocking agent, to a greater extent than are the effects of S-amphetamine [22], the introduction of methoxy and methyl groups may increase the serotonergic effects of amphetamine and thus decrease its rate dependent effects. The serotonergic effects of R– and S–DOM have also been noted in studies with vascular tissue [5].

In summary, R(–) DOM is considerably more potent than S(+) DOM in decreasing schedule controlled responding. The R-isomer has also been reported to be the more potent in producing subjective effects in humans, and it is this isomer which corresponds in absolute configuration to the active isomer of LSD. R,S–DOM was more potent than would be predicted from the activities of the two isomers, and this activity can be attributed to the previously reported stereoselective metabolism of the isomers.

ACKNOWLEDGEMENTS

We would like to thank Dr. Neal Castagnoli, Jr. for kindly providing the drugs used in this study and for his many helpful discussions.

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