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BRIEF COMMUNICATION

The Effect of MDMA ("Ecstasy") and Its Optical Isomers on Schedule-Controlled Responding in Mice

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GLENNON, R. A., P. J. LITTLE, J. A. ROSECRANS AND M. YOUSIF. *The effect of MDMA ("Ecstasy") and its optical isomers on schedule-controlled responding in mice.* PHARMACOL BIOCHEM BEHAV **26**(2) 425–426, 1987.—Eleven mice were trained to respond under an FR 20 schedule of reinforcement and, after learning the schedule, were administered doses of saline and the following phenylisopropylamines: (±)-MDMA, S(+)-MDMA, R(−)-MDMA and (+)-amphetamine. Each of the phenylisopropylamines decreased rates of operant responding in a dose-dependent manner. S(+)-MDMA (ED50=3.1 mg/kg) was nearly equipotent with racemic MDMA and four times more potent than R(−)-MDMA (ED50=4.1 and 11.6 mg/kg, respectively), but less potent than (+)-amphetamine (ED50=0.74 mg/kg). The present study constitutes the first enantiomeric behavioral-potency comparison for the optical isomers of MDMA.

Schedule-controlled responding N-Methyl-1-(3,4-methylenedioxyphenyl)-2-aminopropane MDMA S(+)-MDMA R(−)-MDMA

N - METHYL - 1 - (3,4 - methylenedioxyphenyl) - 2 - amino - propane (i.e., methylenedioxymethamphetamine, MDMA, XTC, "Ecstacy") has recently attracted wide-spread attention because of its potential therapeutic utility in psychiatric disorders and because of its abuse potential [7]. MDMA is an optically active substance, yet, little is known concerning the relative potency of each of the two possible optical isomers. In humans, racemic MDMA produces its central effects at total doses of 75–160 mg; whereas the S(+)-isomer is active at 50–80 mg, no acceptable value has yet been obtained for the R(−)-isomer (although it was speculated, on the basis of preliminary data, to be in the vicinity of 300 mg) [1]. S(+)-MDMA is approximately three times more potent than its R(−)-enantiomer in producing hyperthermia in rabbits [1]; however, neither isomer produces DOM-like stimulus effects in animals trained to discriminate 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (DOM) from saline [2,3], and R(−)-MDMA is three to four times more potent than S(+)-MDMA in binding to central serotonin and dopamine binding sites (although neither isomer displays a significant affinity for these sites) [6]. To date, there is no information available on the relative behavioral potencies of these optical isomers. We report here the effect of racemic MDMA, S(+)-MDMA and R(−)-MDMA on schedule-controlled responding in mice as subjects.

METHOD

Twelve male ICR mice (30–35 g), housed in standard animal facilities with a 12-hr light/dark cycle, were maintained at constant weight by restricting their diet. The animals were trained to respond under an FR 20 schedule of reinforcement in a single-lever operant procedure. The apparatus has already been described in detail [5]. After learning the schedule of reinforcement, the mice were challenged on 5 consecutive days with saline vehicle to establish baseline responding. Subsequently, animals received daily injections of saline except on test days (Tuesdays and Fridays); on these days, the animals would be administered one of the test drugs. Doses of racemic and S(+)-MDMA were evaluated in all 11 animals (one animal died shortly after the study began); doses of R(−)-MDMA and S(+)-amphetamine were evaluated in groups of 5 to 6 mice. Results are expressed as percent of vehicle response rates; vehicle response rate from the day prior to the test session served as control. The order of drug administration was as follows: (a) racemic MDMA, (b) S(+)-MDMA, (c) R(−)-MDMA and (+)-amphetamine (i.e., approximately half of the animals received one drug and half received the other); doses were administered in a random sequence. Solutions of all drugs were made fresh daily in 0.9% sterile saline, and all injections were made by

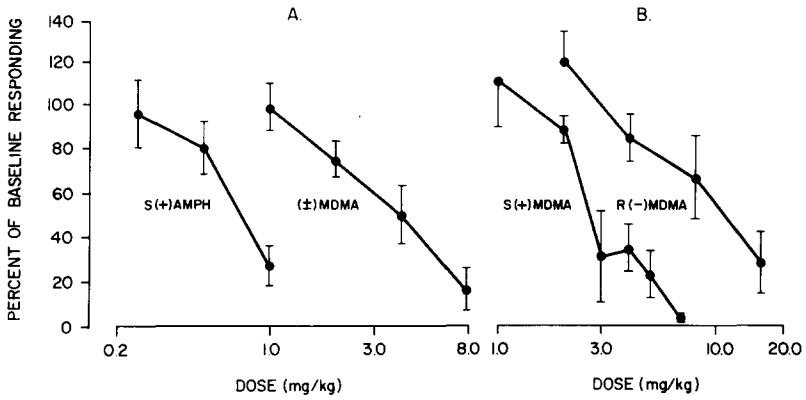

FIG. 1. Effect of various doses of S(+)-amphetamine and racemic MDMA (left panel), and S(+)-MDMA and R(−)-MDMA (right panel), on operant responding with mice as subjects. Percent baseline responding refers to the number of responses made (after drug administration) during a 15-min test session as a percent of the number of responses made after administration of saline in the same animals (n=5–11 animals at each dose).

the intraperitoneal route 15 min prior to a 15-min test session.

Racemic MDMA and its isomers were prepared by acylation of 1-(3,4-methylenedioxyphenyl)-2-aminopropane, or its appropriate optical isomer, with ethyl chloroformate followed by reduction with lithium aluminum hydride and treatment of an ethereal solution of the product with HCl gas. The HCl salts were recrystallized from isopropanol; melting points (degrees C) and optical rotations (10% aqueous solutions at 24°C, where applicable) are as follows: racemic MDMA 151–152°; S(+)-MDMA 184–185°, +13.8°; R(−)-MDMA 183–184°, −13.5°. Melting points are in agreement with those reported by Anderson *et al.* [1]. S(+)-Amphetamine was used as the sulfate salt (Sigma).

RESULTS AND DISCUSSION

Racemic MDMA, S(+)-MDMA, R(−)-MDMA, and S(+)-amphetamine (included for comparative purposes) decreased rates of operant responding in a dose-related manner (Fig. 1). S(+)-MDMA was slightly more potent than racemic MDMA and nearly four times more potent than R(−)-MDMA; ED50 values (followed by 95% confidence limits) are: 3.1 (2.4–4.0), 4.1 (2.8–6.0), and 11.6 (5.3–25.3) mg/kg for S(+)-MDMA, racemic MDMA, and R(−)-MDMA, respectively. S(+)-Amphetamine was more potent [ED50=0.74 (0.44–1.24) mg/kg] than MDMA or either of its isomers.

With MDMA, as with the phenylisopropylamine amphetamine, but in contrast to hallucinogenic phenylisopropylamines (e.g., DOM) [2], the S(+)-isomer is several times more potent than its R(−) enantiomer. This order of potency agrees quantitatively and/or qualitatively with that reported for the isomers of MDMA in the above-mentioned rabbit hyperthermia and human studies, and the 4-fold difference in potency of S(+)-amphetamine relative to racemic MDMA is the same as that obtained in tests of discriminative control of behavior using rats trained to discriminate S(+)-amphetamine from saline. Furthermore, in a separate study, we have recently trained a group of rats to discriminate 1.0 mg/kg of racemic MDMA from saline; here too, the enantiomeric potency ratio for stimulus generalization is 4 (i.e., ED50 values for S(+)- and R(−)-MDMA are 0.23 and 1.0 mg/kg, respectively) ([4], and Glennon, unpublished data). Thus, disruption of schedule-controlled responding of mice might be a useful and convenient method for the investigation of relative potencies of optical isomers within a given chemical/pharmacological class of agents.

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REFERENCES

1. Anderson, G. M., G. Braun, U. Braun, D. E. Nichols and A. T. Shulgin. Absolute configuration and psychotomimetic activity. *NIDA Res Monog* **22**: 8–15, 1978.
2. Glennon, R. A. Discriminative stimulus properties of phenylisopropylamine derivatives. *Drug Alcohol Depend* **17**: 119–134, 1986.
3. Glennon, R. A. and R. Young. Further investigation of the discriminative stimulus properties of MDA. *Pharmacol Biochem Behav* **20**: 501–505, 1984.
4. Glennon, R. A., M. Titeler, R. A. Lyon and M. Yousif. MDMA ("Ecstasy"): Drug discrimination and brain binding properties. *Soc Neurosci Abstr* **12**: 919, 1986.
5. Hendry, J. S. and J. A. Rosecrans. The development of pharmacological tolerance to the effect of nicotine on schedule-controlled responding in mice. *Psychopharmacology (Berlin)* **77**: 339–342, 1982.
6. Lyon, R. A., R. A. Glennon and M. Titeler. 3,4-Methylenedioxyamphetamine (MDMA): Stereoselective interactions at brain 5-HT1 and 5-HT2 receptors. *Psychopharmacology (Berlin)* **88**: 525–526, 1986.
7. WHO Expert Committee on Drug Dependence, Twenty-second Report, WHO Technical Report Series 729, World Health Organization, Geneva, 1985.