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Cocaine—Stimulus Generalization to MDA Optical Isomers: A Reevaluation

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YOUNG, R. AND R. A. GLENNON. *Cocaine—stimulus generalization to MDA optical isomers: A reevaluation.* PHARMACOL BIOCHEM BEHAV **57**(1/2) 115–118, 1997.—It has already been demonstrated that the psychoactive agent 1-(3,4-methylenedioxyphenyl)-2-aminopropane (MDA) produces effects that are both hallucinogen-like and amphetamine- or stimulant-like in animals. Hallucinogenic activity is associated primarily with the R(−)-isomer of MDA whereas stimulant activity is primarily associated with the S(+)-isomer. Because a previous report indicates that S(+)MDA fails to substitute for cocaine in rats trained to discriminate cocaine from vehicle, and because these findings are inconsistent with the purported stimulant nature of S(+)MDA, we reinvestigated the effect of both MDA isomers in rats. In this investigation, S(+)MDA doses of 1.25 and 1.5 mg/kg were found to produce > 80% cocaine-appropriate responding in rats trained to discriminate 8 mg/kg of cocaine from saline. However, consistent with a previous report, R(−)MDA resulted only in partial generalization. These new results support the hypothesis that the optical isomers of MDA produce distinguishable stimulus effects in rats, and that S(+)MDA is the more stmulant isomer of MDA. © 1997 Elsevier Science Inc.

Cocaine MDA S(+)MDA R(−)MDA 1-(3,4-methylenedioxyphenyl)-2-aminopropane

MDA or 1-(3,4-methylenedioxyphenyl)-2-aminopropane is a psychoactive substance that possesses both central stimulant and hallucinogenic character. For example, using a drug discrimination paradigm with rats as subjects we showed, over a decade ago, that MDA substitutes for the stimulant (+)amphetamine in (+)amphetamine-trained animals, and substitutes for the hallucinogen DOM or 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane in animals trained to discriminate DOM from vehicle (7,8). Others have published similar results using rats trained to discriminate (+)-amphetamine (4,9), or the hallucinogen LSD (lysergic acid diethylamide) (1,10), from vehicle. The reverse of these experiments have also been conducted. That is, animals have been trained to discriminate racemic MDA from vehicle, and MDA-stimulus generalization occurs to the hallucinogens DOM and LSD, as well as to the stimulants (+)amphetamine and cocaine (5,6). The R(−)-isomer of MDA seems primarily responsible for the hallucinogenic effects, whereas the S(+)-isomer is primarily responsible for central stimulant activity; that is, DOM-stimulus generalization occurs to R(−)-MDA but not to S(+)MDA, whereas (+)amphetamine-stimulus generalization occurs to S(+)-MDA, but not to R(−)MDA, (7,8). These findings have generally been supported by other groups of investigators. For example, Appel et al (1), and Oberlender and Nichols (10), have shown that R(−)-MDA, but not S(+)MDA, substitutes for LSD in LSD-trained animals. Furthermore, in rats trained to discriminate either R(−)MDA from vehicle, or S(+)MDA from vehicle, the S(+)MDA stimulus completely generalizes to cocaine (1), whereas administration of (+)amphetamine to these same animals results at least in partial (>60%) generalization (3). In contrast, the R(−)MDA stimulus generalizes to LSD and DOM, but not to (+)amphetamine and cocaine (1).

Most recently, we have shown that rats can be trained to discriminate R(−)MDA (1.25 mg/kg) from S(+)MDA (1.25 mg/kg) from saline vehicle in a three-lever operant paradigm (14). Not only is this the first demonstration that optical isomers of the same agent can be discriminated, it lends considerable support to the concept that R(−)MDA and S(+)MDA can produce qualitatively distinguishable behavioral effects. In tests of stimulus generalization using these three-lever trained animals, administration of hallucinogens such as DOM results in the animals making >80% of their responses on the R(−)MDA-appropriate lever in a dose-related fashion, whereas administration of stimulants such as (+)amphetamine or cocaine results in responding on the S(+)MDA-appropriate

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lever (14). Furthermore, consistent with the concept that stimulants and hallucinogens act via distinct mechanisms (that is, stimulants act via a dopaminergic mechanism whereas hallucinogens act as 5-HT2 serotonin agonists) (12,14), the stimulus effect of R(−)MDA, but not those of S(+)MDA, can be antagonized by 5-HT2 antagonists. (3,13).

The results described thus far are fairly consistent. What remains would be to examine the optical isomers of MDA in animals trained to discriminate a different central stimulant (e.g. cocaine) from vehicle. This would lend further support to, or seriously detract from, the concept that S(+)MDA is a central stimulant. That is, the cocaine stimulus might be expected to differentiate between the optical isomers of MDA; R(−)MDA should not substitute, and S(+)MDA might substitute, for cocaine in cocaine-trained animals. Indeed, Broadbent et al (2) have conducted such studies using groups of rats trained to discriminate different doses of cocaine from vehicle. As expected, the R(−)-isomer of MDA failed to produce cocaine-like effects in animals trained to discriminate either 3.5 or 10.0 mg/kg of cocaine from saline (2). Interesting, however, is that although 1 mg/kg of S(+)MDA produced 80% cocaine-appropriate responding in the group of animals trained to discriminate 3.5 mg/kg of cocaine, substitution of S(+)MDA was neither complete nor dose-dependent in the 10 mg/kg trained group (2). Since a 3.5 mg/kg cocaine training dose is lower than that commonly used in drug discrimination studies (2), Broadbent et al (2) entertained the idea that the low training dose of cocaine might have exerted only weak stimulus control of behavior; this could account for the failure to observe stimulus generalization at the higher training dose.

The failure of S(+)MDA to substitute for cocaine in a complete and dose-dependent manner in animals trained to a common training dose of cocaine weakens the argument that S(+)MDA is a central stimulant. Because of the numerous studies suggesting the contrary, and because cocaine has been previously shown to substitute for MDA in rats trained to discriminate racemic MDA from vehicle (6), and for S(+)MDA in rats trained to discriminate S(+)MDA from R(−)MDA (14), we felt that a reevaluation of the effects of S(+)MDA and R(−)MDA in cocaine-trained animals was necessary. The simple purpose of this investigation was to address the question: is there any evidence that S(+)MDA can produce cocaine-like stimulus effects in animals?

METHODS

Six male Sprague–Dawley rats, weighing 250–300 g at the beginning of the study, were trained to discriminate cocaine from saline for sweetened milk reward as previously described in detail (13). Standard two-lever operant chambers (Coulbourn Instruments, model E10-10) housed within light- and sound-attenuating outer chambers were employed. Animals were first trained to respond on both levers. Once lever-pressing behavior was acquired, animals were trained to discriminate IP injections of cocaine (8.0 mg/kg) from 0.9% sterile saline (1.0 ml/kg); that is, rats were trained to respond on a variable-interval 15-s (VI 15) schedule of reinforcement, and once rates of responding stabilized, animals received an injection of drug or saline 15 min prior to each session. Drug or saline was administered on a double-alternation schedule (i.e., 2 days drug, 2 days saline) and training sessions were of 15 min duration. On every fifth day, learning was assessed during an initial 2.5-min nonreinforced (extinction) period followed by a 12.5-min training session. Data collected during the extinction period included percent drug-appropriate lever responding (i.e., the number of responses on the drug designated lever ÷ total number of responses, expressed as a percent) and total responses made during the 2.5-min session (expressed as responses/min).

Once rats consistently (i.e., for 3 consecutive weeks) made >80% of their responses on the drug-appropriate lever after administration of drug and <20% of their responses on the same lever after injection of saline, stimulus generalization studies were begun. During these investigations, test sessions were interposed among the training sessions; however, after the 2.5-min extinction period the animals were returned to their home cages. The animals maintenance injections with cocaine and saline were counterbalanced before test sessions. During generalization tests, rats were injected with doses of MDA isomers and, 15 min later, tested under extinction conditions. Stimulus generalization was said to have occurred when animals made >80% of their responses on the drug-appropriate lever. Drug doses were administered in a random order, unless disruption of behavior occurred (i.e., where the majority of animals failed to make a total of 5 responses during the entire 2.5-min extinction session). Where disruption of behavior occurred, doses between the disruption dose and the highest nondisruptive dose were examined.

Drugs

Cocaine hydrochloride was purchased from Sigma Chemical Co. (St. Louis, MO). (+)MDA hydrochloride and (−)MDA hydrochloride were obtained from NIDA. All solutions were prepared fresh daily and all agents were administered via IP injection in a 1.0-ml/kg injection volume.

RESULTS

Six rats were trained to discriminate 8 mg/kg of cocaine from saline vehicle such that the animals made 93 (±4)% of their responses on the cocaine-appropriate lever following the administration of the training dose of cocaine, and 6 (±2)% of their responses on the same lever following the administration of 1.0 ml/kg of saline. The animals response rates under the cocaine and saline conditions were similar [13.8 (±1.9) and 13.1 (±1.6) responses/min, respectively]. One of the animals died early in the study and the stimulus generalization experiments reflect the results obtained with five animals.

Administration of S(+)MDA doses resulted in a dose-related increase in cocaine-appropriate responding such that after doses of 1.25 and 1.5 mg/kg of S(+)MDA the animals made >80% of their responses on the cocaine-designated lever (Fig. 1). All five animals responded except at the highest two doses where 4/5 and 3/5 animals responded, respectively. The animals' response rates decreased in an orderly fashion, and following 1.5 mg/kg of S(+)-MDA, response rates were reduced to about 50% of saline control. A total of seven doses of R(−)MDA were examined. Dose related increases in cocaine-appropriate responding were observed up to 2.25 mg/kg (i.e. 34%). All five animals responded at 0.25 and 0.5 mg/kg, and 4/5 animals responded at 1.5 and 2.0 mg/kg. Following 2.25 mg/kg of R(−)MDA, only 3/5 animals responded and response rates were reduced to about 40% of control. At 2.5 mg/kg, none of the five animals responded. Subsequent administration of 2.35 mg/kg of R(−)MDA resulted in 40% cocaine-appropriate responding, and response rates were depressed to about 20% of control for the 3/5 animals that responded.

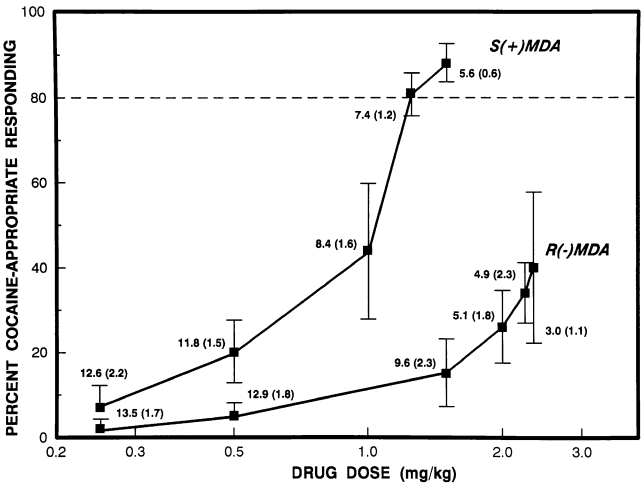

FIG. 1. Mean (± SEM) percent cocaine-appropriate response of various doses of S(+)MDA and R(−)MDA in rats (n=5) trained to discriminate 8 mg/kg of cocaine from saline vehicle. A dose of 8 mg/kg of cocaine resulted in 93% cocaine-appropriate responding. Values associated with each data point represent response rates (responses/min) followed in parenthesis by SEM. The highest dose of R(−)MDA examined (2.5 mg/kg; data not shown) resulted in disruption of behavior (i.e., none of the animals made ≥ 5 responses during the entire 2.5-min extinction session).

DISCUSSION

On the basis of previously published drug discrimination studies, it would seem that R(−)MDA is more hallucinogen-like than stimulant, and that S(+)MDA is more stimulant than hallucinogen-like (see introduction). Consistent with this concept, cocaine substitutes for the training drug both in MDA-trained animals (6) and in S(+)MDA-trained animals (1). A significant inconsistency is that substitution of S(+)MDA was neither complete nor dose-dependent in animals trained to discriminate a common cocaine training dose (i.e., 10 mg/kg) from vehicle. This latter finding, at least in part, has led Broadbent et al (2) to argue that S(+)MDA may not be a stimulant-like agent. Because the putative behavioral similarity or dissimilarity between S(+)MDA and cocaine is a central issue in understanding the pharmacology of MDA and MDA-related designer drugs, it was felt important to re-examine the optical isomers of MDA in cocaine-trained animals. We have previously used a cocaine training dose of 8 mg/kg in some of our studies (e.g. 13), and for purpose of comparison we continued to use this same training dose.

Figure 1 shows that R(−)MDA elicits a maximum of 40% cocaine-appropriate responding at 2.35 mg/kg; a somewhat higher R(−)MDA dose (2.5 mg/kg) produced disruption of behavior with none of the animals responding. These results are reasonably consistent with those of Broadbent et al (2) where R(−)MDA also produced only partial generalization. In contrast to the latter study, however, is that S(+)MDA completely (i.e. >80% drug-appropriate responding) and dose-dependently substituted for cocaine (Fig. 1). As in the Broadbent study, the animals' response rates progressively fell as the S(+)MDA dose was increased. This is not wholly unexpected, because both isomers of MDA are known to produce a stimulus effect similar to that of the nonstimulant, nonhallucinogenic designer drug analog MBDB (*N*-methyl-1-(1,3-benzodioxol-5-yl)-2-butanamine) (11). Moreover, at doses where S(+)MDA-stimulus generalization occurred to cocaine, the animals' response rates were also significantly depressed (14). Thus, the animals' depressed response rates may be accounted for by the MBDB-like action of the MDA optical isomers.

How can the differences between the present study and that of Broadbent et al (2) be explained? There are several possible explanations: the two studies used different training doses of cocaine (8 mg/kg versus 10 mg/kg) and different schedules of reinforcement. Either factor, alone, could account for the observed differences. Another explanation is that the dose-response relationship in the Broadbent study is incomplete. For example, 1 mg/kg of S(+)MDA produced 82% cocaine-appropriate responding (i.e., stimulus generalization) with eight of eight animals completing the session; higher doses resulted in depressed response rates and, eventually, in disruption of behavior. This latter effect is not unlike what was observed in the present investigation.

In summary, then, we have shown that a cocaine stimulus generalizes to S(+)MDA but not to R(−)MDA. As previously reported (2), administration of R(−)MDA to cocaine-trained animals resulted only in partial generalization. Although Broadbent et al (2) demonstrated that S(+)- MDA can produce 82% cocaine-appropriate responding in rats trained to discriminate 10 mg/kg of cocaine from vehicle, they were unable to demonstrate stimulus generalization in a dose-dependent manner. The results shown in Fig. 1 suggest that stimulus generalization can occur in a dose-dependent fashion. Overall then, on the basis of the present investigation, as well as on those employing the three-lever paradigm with animals trained to discriminate R(−)MDA from S(+)MDA from vehicle (14), it would appear that the two optical isomers of MDA are capable of producing distinguishable stimulus effects in rats with R(−)MDA being the more hallucinogenic isomer, and S(+)MDA the more stimulant isomer.

ACKNOWLEDGEMENTS

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