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MDA: AN AGENT THAT PRODUCES STIMULUS EFFECTS SIMILAR TO THOSE OF 3,4-DMA, LSD AND COCAINE

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1-(3,4-Methylenedioxyphenyl)2-aminopropane (3,4-methylenedioxyamphetamine; 3,4-MDA) is a substituted phenylisopropylamine with abuse potential (the 'Love Drug'); its effect in humans has been characterized as being both LSD-like and amphetamine-like (Shulgin, 1978). Amphetamine and 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (DOM) are also phenylisopropylamine derivatives; whereas amphetamine is a central stimulant, DOM is hallucinogenic in man (Shulgin, 1978). All three agents serve as discriminative stimuli in animals; while the amphetamine stimulus does not generalize to DOM, and the DOM stimulus does not generalize to amphetamine, 3,4-MDA appears to mimic both agents (regardless of which of the three agents is used as the training drug) (Glennon and Young, 1984). In other words, 3,4-MDA seems to be a psychoactive agent with dual stimulus properties. We have recently found that the S(+)-isomer of 3,4-MDA is responsible for the amphetamine-like stimulus properties of this agent, while the R(−)-isomer possesses DOM-like effects (Glennon and Young, 1984). This explains some of the previous difficulty of classifying 3,4-MDA as either a central stimulant or as a hallucinogenic agent.

We are currently using the drug discrimination paradigm (a) to investigate the structure-activity relationships and mechanisms of action of psychoactive agents, and (b) to determine if a similarity exists between the discriminative stimulus properties of these agents and their activity/potency in humans. To this extent, we have reported that the DOM-like stimulus properties of a series of over thirty hallucinogenic agents correlates significantly with their human potency (Glennon et al., 1982). Using the drug discrimination paradigm with animals trained to discriminate 3,4-MDA from saline, we are afforded the opportunity to further investigate the unique properties of this agent.

The phenylisopropylamine derivative 1-(3,4-dimethoxyphenyl)-2-aminopropane (3,4-DMA) reportedly produces psychotomimetic effects in man but is several-fold less active than 3,4-MDA (Shulgin, 1978); yet neither an amphetamine-stimulus (unpublished results) nor a DOM-stimulus (Glennon et al., 1982) generalizes to 3,4-DMA. Thus, this agent may possess unique properties of its own. As another example, there is a report in the lay literature that likens the effects of 3,4-MDA to 'those produced by a combination of cocaine and [LSD]' (Stafford, 1977); however, the discriminative stimulus (as well as other) effects of cocaine and LSD are known to be quite dissimilar (Silverman and Ho, 1977). The purpose of this current study was to further characterize the stimulus properties of 3,4-MDA, and to explore the effects that might have a bearing on the attractiveness of this agent as a drug of abuse.

Employing Sprague-Dawley rats (n = 7) trained to discriminate 1.5 mg/kg of 3,4-MDA hydrochloride from saline, using standard operant procedures, under a variable interval 15-s schedule of reinforcement for food reward (Glennon and Young, 1984), doses of 3,4-DMA hydrochloride, (+)-LSD tartrate monomethanolate and cocaine hydrochloride were administered in a random sequence in tests of stimulus generalization. All drugs

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TABLE 1

Results of generalization studies using rats trained to discriminate 1.5 mg/kg of MDA HCl from saline.

Agent	Dose (mg/kg)	N [a]	MDA-appropriate responding [b] (±S.E.M.)	Resp/min [b] (±S.E.M.)
3,4-DMA	5.0	7/7	20% (6.1)	10.0 (1.5)
	5.25	3/3	42% (12.6)	9.6 (1.8)
	5.5	4/4	59% (16.3)	7.3 (1.7)
	5.85	7/7	71% (10.6)	8.2 (1.6)
	6.0	2/3	96% (4.0)	6.2 (2.1)
	6.25	1/4	–	
	7.5	1/4	–	
		ED_{50} = 5.36 (5.11-5.66) mg/kg [c]		
LSD	0.05	4/4	31% (11.1)	10.3 (2.2)
	0.06	4/4	53% (20.1)	7.8 (1.9)
	0.075	3/4	86% (4.1)	6.3 (2.9)
		ED_{50} = 0.058 (0.045-0.074) mg/kg [c]		
Cocaine	4.0	4/4	33% (14.8)	11.0 (2.4)
	6.0	4/4	46% (14.6)	9.5 (2.5)
	8.0	4/4	47% (13.3)	9.8 (2.7)
	9.0	3/4	67% (22.4)	5.7 (1.5)
	9.15	3/4	94% (5.6)	5.8 (2.1)
		ED_{50} = 5.87 (3.84-8.97) mg/kg [c]		
3,4-MDA [d]		ED_{50} = 0.65 mg/kg		
Saline (1 ml/kg)		7/7	7% (2.6)	13.8 (1.7)

[a] Number of animals responding/number of animals receiving drug. [b] Data obtained during 2.5-min extinction session. [c] ED_{50} value followed in parentheses by 95% confidence limits. [d] Data previously reported (Glennon and Young, 1984); included for comparative purposes.

were dissolved in sterile saline and were administered by intraperitoneal injection 15 min prior to a 2.5-min extinction session. Table 1 reveals that 3,4-MDA-stimulus generalization occurred to all three agents. At the doses at which generalization occurred, response rates were reduced to approximately 50% of those following saline administration. Although 3,4-DMA produces stimulus effects that differ from those produced by amphetamine or DOM, these effects are apparently similar to those produced by 3,4-MDA. The MDA-trained animals also recognize LSD (to which a DOM stimulus but not an amphetamine stimulus generalizes) and cocaine (to which an amphetamine but not an LSD stimulus generalizes). These results suggest that 3,4-MDA may possess a rather complex mechanism of action, and support our previous findings that 3,4-MDA is capable of producing a dual stimulus effect in animals. Furthermore, the similarity between the stimulus effects of 3,4-MDA and those of central stimulants (e.g. amphetamine and cocaine) and hallucinogenic agents (e.g. DOM and LSD) may account for its abuse potential.

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