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BRIEF COMMUNICATION

Stimulus Properties of Ring-Methyl Amphetamine Analogs

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HIGGS, R. A. AND R. A. GLENNON. *Stimulus properties of ring-methyl amphetamine analogs*. PHARMACOL BIOCHEM BEHAV **37**(4) 835–837, 1990.—There are three possible ring-substituted methyl amphetamines (or tolylaminopropanes; TAPs): oTAP, mTAP and pTAP. These agents are positional isomers of methamphetamine. Although all three isomers have been previously reported to possess amphetamine-like character, few studies have examined all three agents in comparison with (+)amphetamine. Using rats trained to discriminate 1 mg/kg of (+)amphetamine from saline under a variable-interval 15-sec schedule of reinforcement, tests of stimulus generalization were conducted with the three positional isomers. Only oTAP (ED_{50} dose = 4.1 mg/kg) completely substituted for (+)amphetamine. mTAP and pTAP resulted only in partial (ca. 50% amphetamine-appropriate responding) generalization. It is concluded that oTAP is capable of producing amphetamine-like stimulus effects and that it is approximately one-tenth as potent as (+)amphetamine; however, because the partial generalization produced by mTAP and pTAP was followed by disruption of behavior at slightly higher doses, it cannot be reliably stated that these latter two isomers lack amphetamine-like character.

Stimulus properties Ring-methyl amphetamine analogs Amphetamine Methylamphetamine

THE two most widely abused clandestinely synthesized drugs in the United States are amphetamine and methamphetamine (13), and in the last several years, a crystalline form of methamphetamine ("ice") has become increasingly popular. Whereas the terms methamphetamine or methylamphetamine are commonly employed to refer only to the N-methyl analog of amphetamine, there are also possible three methyl amphetamine analogs where the methyl group is attached directly to the aromatic ring rather than to the terminal amine of amphetamine. These tolylaminopropane (TAP) derivatives are positional isomers of methamphetamine with the methyl substituent being either at the 2- (oTAP), 3- (mTAP), or 4-position (pTAP) of the aromatic ring. In the past, there have been sporadic reports of the abuse of ring-methylated amphetamines [see Shulgin (15) for a brief review]. Interestingly, however, relatively little has been reported on these structurally simple derivatives of amphetamine.

In a Sidman avoidance schedule using rats, doses of 5 and 10 mg/kg of pTAP produce a "low-dose stimulant profile, and a high-dose stimulant profile," respectively (2); amphetamine was not included in these studies for comparison. In contrast, Cox and Maikel (4) report that pTAP behaves as a depressant of avoidance responding in rats. However, it seems that at low doses, pTAP is a more potent stimulant than amphetamine (10,12), whereas at higher doses, this stimulant effect disappears (10). As with amphetamine, pTAP produces hyperthermia in several species of animals (1,12) and appears to be at least as potent as amphetamine. pTAP also produces amphetamine-like electroencephalographic patterns in cats (1). Few studies have compared all three TAP isomers. mTAP is somewhat more potent than oTAP and pTAP as a sympathomimetric agent (3). Both oTAP and mTAP are more potent than pTAP as locomotor stimulants in mice (14). Although examined only at low doses (i.e., doses that did not exceed 2 mg/kg), both oTAP and mTAP produce mild central stimulant effects in humans (11).

The purpose of the present investigation was two-fold: (a) to evaluate and compare the discriminative stimulus effects of all three positional isomers of TAP in rats trained to discriminate 1 mg/kg of S(+)amphetamine sulfate from saline, and (b) to challenge established structure-activity relationships (SAR). Structure-activity relationships formulated for amphetamine-like activity have concluded that aromatic ring-substitution decreases significantly, and in some cases abolishes, amphetamine-like character (6). On the other hand, N-methylation is one of the few structural modifications that actually enhances the potency of amphetamine (6). If, as suggested by some of the pharmacological data cited above, TAP isomers are as potent or more potent than amphetamine, these SAR would be in need of revision.

METHOD

Eight male Sprague-Dawley rats (200–300 g) were trained to discriminate intraperitoneal injections of 1.0 mg/kg of (+)amphetamine sulfate from 1.0 ml/kg of 0.9% sterile saline for food (sweetened powdered milk) reward using a variable-interval 15-sec schedule of reinforcement. Standard two-lever operant

TABLE 1

RESULTS OF STIMULUS GENERALIZATION STUDIES WITH TAP ISOMERS IN (+)AMPH-TRAINED RATS

Agent	Dose (mg/kg)	N*	Percent AMPH Responding†	Response Rate‡	ED_{50} Dose (mg/kg)§
oTAP	0.2	3/3	4 (±2)	7.7 (±2.7)	
	0.5	3/3	35 (±10)	8.5 (±2.6)	
	2.0	3/4	19 (±16)	10.5 (±3.0)	
	3.5	4/4	25 (±23)	11.9 (±2.3)	
	5.0	4/4	45 (±23)	6.2 (±2.5)	
	8.0	5/8	87 (±12)	5.2 (±1.3)	4.1 (1.2–13.8)
mTAP	0.3	3/4	0	13.0 (±1.2)	
	1.0	2/4	14 (±14)	20.2 (±9.4)	
	1.5	4/6	46 (±22)	13.2 (±8.1)	
	1.7	1/3	—¶		
	2.0	1/4	—		
pTAP	0.5	3/4	5 (±4)	12.2 (±2.6)	
	0.8	3/5	26 (±18)	14.3 (±1.5)	
	1.0	5/7	49 (±18)	9.2 (±3.1)	
	1.1	1/4	—¶		
	1.3	1/3	—		
	1.4	1/4	—		
	2.0	0/4	—		
(+)AMPH	1.0	8/8	92 (±3)	13.1 (±2.8)	0.42#
Saline (1 ml/kg)		8/8	9 (±4)	13.8 (±4.3)	

*Number of animals responding/number receiving drug.

†Percent of total responses made on the AMPH-appropriate lever. Data collected during the 2.5-min extinction session.

‡Responses per min during the 2.5-min extinction session.

§ED_{50} value followed by 95% confidence limits.

¶Disruption of behavior; majority of animals failed to make at least 5 responses during the entire 2.5-min extinction session.

#ED_{50} value previously reported (8); included only for comparison.

chambers (Coulbourn Instruments model E10-10) were employed. The animals used in this study are the same that were used in a previous investigation and the details of their training have already been reported (7). During the stimulus generalization studies, maintenance of the drug/saline discrimination was insured by continuing the 15-min training sessions throughout this period. Training sessions were conducted with (+)amphetamine sulfate or saline for four days prior to a generalization test session. During the training days, the animals received either (+)amphetamine sulfate or saline and the proper responses were reinforced during a 15-min training period. Once per week, the animals' learning would be assessed by allowing them to respond under each of the two conditions during a nonreinforced 2.5-min extinction session, followed by an additional 12.5-min training session. Animals making >20% of their responses on the saline lever after administration of 1.0 ml/kg of saline or <80% of their responses on the drug-appropriate lever after administration of 1.0 mg/kg of (+)amphetamine sulfate were not used in the subsequent stimulus generalization session. During the stimulus generalization tests, doses of the TAP isomers were administered in a random order (with the proviso that only lower doses of an agent would be examined once disruption of behavior was observed); the animals were allowed 2.5 min to respond under extinction conditions and were then removed to their individual home cages. Criterion for stimulus generalization was ≥80% of total responses on the (+)amphetamine appropriate lever. Disruption of behavior was considered to have occurred when an animal made fewer than 5 total responses during the 2.5-min extinction session. Where stimulus generalization occurred, an ED_{50} dose was calculated by the method of Finney (5); the ED_{50} value represents the dose at which the animals would be expected to make 50% of their responses on the drug-appropriate lever.

S(+)Amphetamine sulfate was purchased from Sigma (St. Louis, MO). The TAP isomers [i.e., oTAP, mTAP, and pTAP; 1-(X-methylphenyl)-2-aminopropane, where X = 2, 3, or 4, respectively], as their HCl salts, were synthesized in our laboratories. All solutions were made fresh daily in 0.9% sterile saline and all injections were made via the intraperitoneal route 15 min prior to testing.

RESULTS AND DISCUSSION

Results of the stimulus generalization studies with the TAP isomers are shown in Table 1. oTAP substituted for (+)amphetamine at a dose of 8.0 mg/kg; at this dose, the animals' response rates were approximately 40% of control rates. The (+)amphetamine-stimulus did not generalize to either mTAP or pTAP; at 1.5 and 1.0 mg/kg, respectively, both agents produced just under 50% (+)amphetamine-appropriate responding and slightly higher doses resulted in disruption of behavior. The results with pTAP are

consistent with what has been reported previously; Huang and Ho (9) found that administration of pTAP to amphetamine-trained rats produces a maximum of 52% amphetamine-appropriate responding.

Evidently, only one of the three TAP isomers, oTAP, seems to result in complete stimulus generalization in the (+)amphetamine-trained animals, and this isomer is only one-tenth as potent as (+)amphetamine. However, because mTAP and pTAP result in partial generalization followed by disruption of behavior, it cannot be concluded that they lack amphetamine-like character. Clearly, though, they seem to produce some other effect that is disruptive to the animals. This effect might conceivably obscure any amphetamine-character that could have been observed had disruption of behavior not occurred; therefore, it seems that use of the drug discrimination paradigm is not the most effective method to determine whether or not these agents are amphetamine-like. Nevertheless, with regard to structure-activity relationships, there is no evidence from these studies that any of the TAP isomers is more potent than amphetamine in producing amphetamine-like stimulus effects in rats.

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