Pharmacology Biochemistry and Behavior, Vol. 58, No. 4, pp. 1109–1116, 1997

0091-3057/97 $17.00 + .00

ELSEVIER

PII S0091-3057(97)00323-7

Cathinone: An Investigation of Several *N*-Alkyl and Methylenedioxy-Substituted Analogs

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Received 24 October 1996; Revised 21 March 1997; Accepted 2 April 1997

DAL CASON, T. A., R. YOUNG AND R. A. GLENNON. *Cathinone: An investigation of several* N*-alkyl and methylenedioxy-substituted analogs.* PHARMACOL BIOCHEM BEHAV **58**(4) 1109–1116, 1997.—Structurally, methcathinone is to cathinone what methamphetamine is to amphetamine. Due to increased interest in the abuse of such agents we wished to determine if certain derivatives of cathinone would behave in a manner consistent with what is known about their amphetamine counterparts; that is, can amphetamine structure–activity relationships be extrapolated to cathinone analogs? As expected on the basis of known structure–activity relationships for amphetaminergic agents, both *N*-monoethylcathinone and *N*-mono-*n*-propylcathinone (N-Et CAT and N-Pr CAT; ED_{50} = 0.77 and 2.03 mg/kg, respectively) produced amphetamine-like stimulus effects in rats trained to discriminate 1 mg/kg of (+)amphetamine from vehicle and were somewhat less potent than racemic methcathinone. In contrast, (−)*N*,*N*-dimethylcathinone or (−)Di Me CAT (ED_{50} = 0.44 mg/kg) was more potent than expected; although (+)*N*,*N*-dimethylamphetamine is sevenfold less potent than (+)methamphetamine, (−)Di Me CAT is only about 1.6-fold less potent than (−)methcathinone, and is essentially equipotent with (−)cathinone. In addition, although it has been previously demonstrated that 1-(3,4-methylenedioxyphenyl)-2-aminopropane (MDA) results in stimulus generalization in rats trained to discriminate (+)amphetamine or DOM from vehicle, the cathinone counterpart of MDA (i.e., MDC) resulted in partial (maximum: 58%) generalization in (+)amphetamine-trained animals, and failed to produce >7% DOM-appropriate responding in rats trained to discriminate DOM from vehicle. On the other hand, the *N*-methyl analog of MDC (i.e., MDMC) behaved in a manner similar to that of the *N*-methyl analog of MDA (i.e., MDMA); that is, a (+)amphetamine stimulus (MDMC: ED_{50} = 2.36 mg/kg) but not a DOM stimulus generalized to MDMC. In MDMA-trained rats, stimulus generalization occured both to MDC and MDMC (ED_{50} = 1.64 and 1.60 mg/kg, respectively). Although this and previous studies have demonstrated that significant parallelisms exist between the structure–activity relationships of amphetamine analogs and cathinone analogs, we now report several unexpected qualitative and/or quantitative differences. It is suggested that caution be used in attempting to draw conclusions or make predictions about the activity and potency of novel cathinone analogs by analogy to the structure–activity relationships derived from amphetamine-related agents; it would appear that each new cathinone analog will require individual investigation. © 1997 Elsevier Science Inc.

Methcathinone Cathinone Amphetamine Methamphetamine MDA MDMA Designer drugs

CATHINONE, one of the centrally acting constituents of the plant *Catha edulis* (33), is a potent central stimulant and is a naturally occurring analog of amphetamine. The only structural difference between cathinone and amphetamine is the presence of a benzylic keto group in the former agent. (+)Amphetamine is several times more potent than its (−)-enantiomer as a central stimulant, whereas (−)-cathinone is several times more potent than its (+)-isomer (9). Although this apparent inconsistency initially caused some confusion, it is now realized that the absolute configuration of (+)amphetamine (i.e., *S*) is identical with the absolute configuration of (−)cathinone (31) (see Fig. 1); that is, *S*(−) cathinone is the stereochemical equivalent of *S*(+)amphetamine. In the course of our investigations of the structure–activity relationships of phenylisopropylamine stimulants, we reasoned that if *N*-monomethylation of amphetamine to methamphetamine is one of the few molecular modifications that results in retention of central stimulant potency, the corresponding *N*-monometh-

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ylation of cathinone should also result in an active compound if cathinone is indeed a naturally occurring relative of amphetamine. We prepared the *N*-monomethyl compound and, by analogy to methamphetamine, termed it methcathinone (19). As expected, methcathinone was found to be several times more potent than cathinone as a locomotor stimulant in mice; in tests of stimulus generalization with rats trained to discriminate (+)amphetamine from vehicle, methcathinone was shown to be about twice as potent as cathinone (ED_{50} = 0.37 and 0.71 mg/kg, respectively) (19). We also demonstrated that methcathinone is capable of inducing the release of radioactivity from (^{3}H)dopamine-prelabeled tissue of rat caudate nucleus in a manner consistent with that observed for cathinone, amphetamine, and methamphetamine (19).

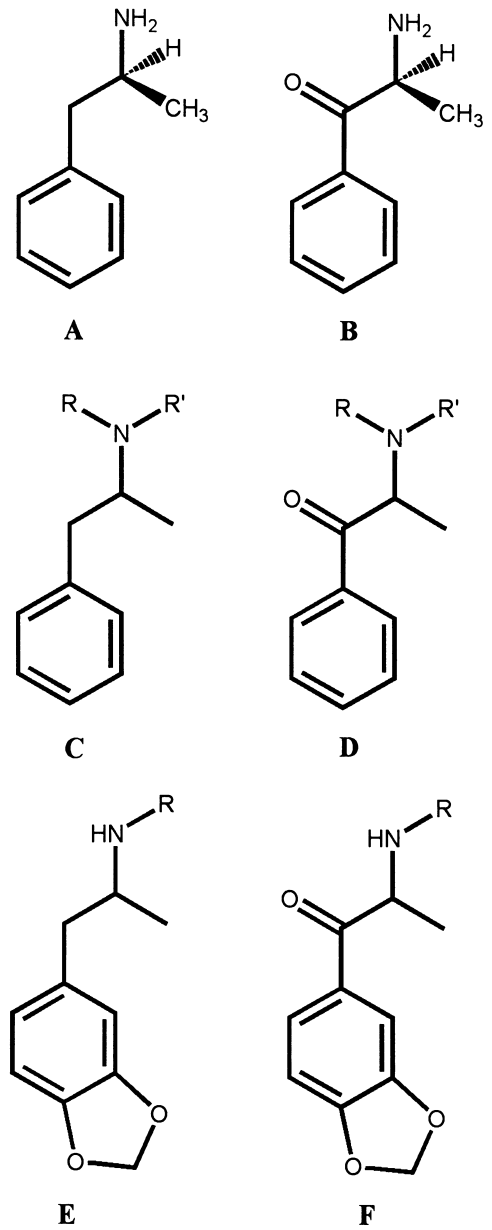

FIG. 1. Chemical structures of S(+)amphetamine (A), S(−)Cathinone (B), *N*,*N*-dimethylamphetamine (Di Me AMPH; C where R = R′ = Me), N-Ethylcathinone (N-Et CAT; D where R = H, R = Et), *N*-*N*-Propylcathinone (N-Pr CAT; D where R = H, R′ = nPr), *N*,*N*-Dimethylcathinone (Di Me CAT; D where R = R′ = Me), 1-(3,4-methylenedioxyphenyl)-2-aminopropane (MDA; E where R = H), *N*-Methyl-1-(3,4-methylenedioxyphenyl)-2-aminopropane (MDMA; E where R = Me), 1-(3,4-Methylenedioxy)cathinone (MDC; F where R = H), and 1-(3,4-methylenedioxy)methcathinone (MDMC; F where R = Me).

Unbeknownst to us at the time, due to the absence of published information, was that methcathinone was a rather popular drug of abuse in the former Soviet Union. Evidently, methcathinone abuse was first identified in Leningrad in 1982 but not reported until years later (30). Methcathinone, referred to in Soviet Union countries as ephedrone, is known clandestinely by several different names (e.g. "effendi," "mul'ka," "pomimutka," "cosmos," "jeff") (30,41). In the late 1980s and early 1990s, methcathinone became a novel drug of abuse in the United States and was eventually classified as a Schedule I substance in 1992 (3); since then, >70 laboratories manufacturing this substance have been seized (5). Methcathinone, known on the street as "cat," seems to be most popular in the mid-West. As might be expected, its effects in humans resemble those of amphetamine (5,6). Its scheduling, coupled with its high potency as a stimulant, prompted us to continue our investigations with methcathinone. We subsequently demonstrated that cocaine-stimulus generalization occurs to methcathinone in rats trained to discriminate cocaine from vehicle and that methcathinone is twice as potent as cathinone (38). We later examined the two optical isomers of methcathinone and found that both are active but that *S*(−)methcathinone is three to five times more potent than *R*(+)methcathinone (a) in tests of stimulus generalization in (+)amphetamine-trained rats, (b) in tests of stimulus generalization in cocaine-trained rats, and (c) as a locomotor stimulant in mice (18). Kaminski and Griffiths have shown that methcathinone is also self-administered by baboons (25).

The basic structural skeleton of amphetamine represents a phenylisopropylamine (i.e., 1-phenyl-2-aminopropane) moiety; stuctural modification of phenylisopropylamines can result in central stimulant, hallucinogenic, and other activities (9). Relatively little is known about the effect of structural modification of cathinone on activity. This raises the question: will structural modification of cathinone parallel the effects observed upon structural modification of amphetamine? We first explored the effect of the optical isomers of cathinone about 15 years ago (13); since then, we have initiated an examination of the structure–activity requirements of cathinone-related agents necessary to produce amphetamine-like behavioral effects in animals. These investigations have primarily employed tests of stimulus generalization using rats trained to discriminate (+)amphetamine from vehicle [e.g., (8)] and have also used rats trained to discriminate cathinone from vehicle [e.g., (15) and references therein]. Most of our efforts have been focused on methcathinone or on structurally simplified analogs of cathinone. Due to the possibility that other cathinone analogs might ultimately appear on the illicit market as new designer drugs, we have continued our structure–activity studies with cathinone-related agents. We were interested in identifying other similarities and potential differences between the structure–activity relationships of the two series of agents.

Methamphetamine is generally considered to be a potent stimulant; however, further homologation of the methyl group to longer alkyl substituents (e.g., ethyl, propyl) results in a progressive decrease in potency (9,34,36,37). The *N*-ethyl and *N*-*n*-propyl derivatives of cathinone were of particular interest because it has been shown that the corresponding *N*-ethyl

and *N*-*n*-propyl derivatives of certain other abused amphetamine-related designer drugs (e.g., analogs of MDA; see below) retain behavioral activity [e.g., (10)]. *N*-Methylation of methamphetamine to afford *N*,*N*-dimethylamphetamine results in a substantial decrease in amphetamine-like activity and potency [e.g., (11,35)]. Thus, we wished to determine if the corresponding structural changes in cathinone would result in effects that parallel those observed with amphetamine. Accordingly, we prepared *N*-monoethylcathinone (N-Et CAT), *N*-mono-*n*-propylcathinone (N-Pr CAT), and *N*,*N*-dimethylcathinone (Di Me CAT) for evaluation in rats trained to discriminate (+)amphetamine from vehicle.

Certain structural modifications of phenylisopropylamines, as mentioned above, can change the nature of the effect produced by the resulting agent. The 3,4-methylenedioxy analog of amphetamine (i.e., 1-(3,4-methylenedioxyphenyl)-2-aminopropane, also known as methylenedioxyamphetamine, 3,4-MDA, or MDA), and its *N*-monomethyl analog MDMA ("Ecstasy"), possess interesting properties. MDA is a central stimulant and a hallucinogenic agent, and stimulus generalization occurs with MDA in groups of animals trained to discriminate (+)amphetamine from vehicle and the phenylisopropylamine hallucinogen DOM (i.e., 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane) from vehicle [e.g., see Young and Glennon (39), and references therein for discussion]. MDMA is considered an empathogen or an agent that facilitates communication and heightens feelings of empathy (1,29); MDMA seems to retain some amphetamine-like character but is not generally considered to be hallucinogenic (10,29). Interestingly, stimulus generalization to MDA is also seen using rats trained to discriminate MDMA from vehicle, suggesting that MDA possesses some MDMA-like qualities (10,29). Because introduction of a benzylic keto group to amphetamine results in retention of amphetamine-like activity and potency, we wished to determine what effect the corresponding molecular modification would have on MDA and MDMA. Hence, we prepared 3,4-methylenedioxycathinone (MDC) and 3,4-methylenedioxymethcathinone (MDMC) for evaluation in rats trained to discriminate either (+)amphetamine, DOM, or MDMA from vehicle.

METHOD

Drug Discrimination Studies

Nine male Sprague–Dawley rats (ca. 250–300 g), housed individually, were reduced in body weight to approximately 80% of their free-feeding weight. During the entire course of the study, the animals' body weights were maintained at this level by partial food deprivation; in their home cages, the animals were allowed drinking water ad lib. The animals were trained (15-min training session) to discriminate intraperitoneal injections (15-min presession injection interval) of 1.0 mg/kg of (+)amphetamine sulfate from vehicle (sterile 0.9% saline) under a variable-interval 15-s schedule of reinforcement for appetitive (sweetened powdered milk) reward. Standard two-lever operant chambers (Coulbourn Instruments model E10-10) were used. In general, daily training sessions were conducted with (+)amphetamine or 1.0 ml/kg of saline; on every fifth day, learning was assessed during an initial 2.5-min nonreinforced (extinction) session followed by a 12.5-min training session. For approximately half the animals, the left lever was designated the drug-appropriate lever, whereas the situation was reversed for the remaining animals. Data collected during the extinction session included responses per minute (i.e., response rate) and number of responses on the drug-appropriate lever (expressed as a percent of total responses). Animals were not used in stimulus generalization studies until they made >80% of their responses on the drug-appropriate lever after administration of training drug, and <20% of their responses on the same drug-appropriate lever after administration of saline, for 3 consecutive weeks. The animals were placed in the operant chambers no more than once per day and were in their home cages except during training and extinction sessions. Five of the animals are those that were used in a recent study and had received the amphetamine analog clobenzorex in tests of stimulus generalization (40); four additional animals were trained as described above and added to the group.

Separate groups of rats were trained, as described above, to discriminate IP administration of DOM (1.0 mg/kg; $n = 7$) or MDMA (1.5 mg/kg; $n = 8$) from saline vehicle. We have previously used animals trained to these two agents and have described the training procedure in detail [e.g., (12,17)].

Tests of stimulus generalization were conducted to determine if the challenge drugs would substitute for the various training drugs. During this phase of the study, maintenance of the training drug discrimination was insured by continuation of the training sessions on a daily basis (except on a generalization test day; see below). On one of the two days before a generalization test, approximately half of the animals would receive training drug and half would receive saline; after a 2.5-min extinction session, training was continued for 12.5 min. Animals not meeting the original criteria (i.e., >80% of total responses on the drug-appropriate lever after administration of training drug and <20% of total responses on the same lever after administration of saline) during the extinction session were excluded from the immediately subsequent generalization test session. During the investigations of stimulus generalization, test sessions were interposed among the training sessions. The animals were allowed 2.5 min to respond under nonreinforcement conditions; the animals were then removed from the operant chambers and returned to their home cages. An odd number of training sessions (five) separated any two generalization test sessions. Doses of the challenge drugs were administered in a random order, using a 15-min presession injection interval. Stimulus generalization was said to have occurred when the animals, after a given dose of challenge drug, made ⩾80% of their responses on the drug-appropriate lever. Animals making fewer than five total responses during the 2.5-min extinction session were considered as being disrupted. ED_{50} values (i.e., doses where the animals would be expected to make 50% of their responses on the drug appropriate lever) were calculated by the method of Finney (7). Solutions of all drugs were prepared fresh daily using 0.9% sterile saline. All drugs were administered via intraperitoneal injection 15 min prior testing.

Drugs

(+)Amphetamine sulfate and (+)*N*,*N*-dimethylamphetamine hydrochloride (Di Me AMPH) (11) were available from previous studies; racemic 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane hydrochloride (DOM) was a gift from NIDA, and racemic *N*-methyl-1(-3,4-methylenedioxyphenyl)-2-aminopropane hydrochloride (MDMA) was synthesized as previously reported (16). The other compounds were synthesized as described below.

Synthesis

(±)*N*-Monoethylcathinone (N-Et CAT), (±)*N*-mono-*n*-propylcathinone (N-Pr CAT), and (±)*N*,*N*-dimethylcathi-

none (Di Me CAT) were prepared as their hydrochloride salts from 2-bromopropiophenone (Aldrich Chemical Co., Milwaukee, WI) by reaction with the appropriate aqueous amine (free base) in a 1 to 2 molar ratio. A general procedure, as adapted from the literature (23), will suffice. Previously chilled (5°C) bromopropiophenone (0.42 mol) was added in a dropwise manner over a 30-min period to a stirred solution of the aqueous amine (free base, 0.85 mol) immersed in an ice-salt (−8°C) bath. The reaction mixture was stirred for 2 h and then allowed to come to room temperature. The mixture was extracted with tap water (4 × 100 ml) to remove any free amine or amine salt. An additional quantity of water (100 ml) and sufficient hydrochloric acid were added to the washed reaction mixture to achieve pH 2. The solution was reextracted with chloroform (4 × 100 ml) to remove any unreacted starting materials. Dilute cold sodium hydroxide solution was added to ad-

TABLE 1

RESULTS OF STIMULUS GENERALIZATION STUDIES IN RATS TRAINED TO DISCRIMINATE (+)AMPHETAMINE (1.0 mg/kg) FROM VEHICLE

Agent	Dose (mg/kg)	n*	%AMPH-Appropriate Responding (±SEM)†	Response Rate, resp/min (±SEM)†	ED_{50} (95% CL)
(+)Amphetamine	0.25	6/6	28% (9)	16.5 (4.2)	
	0.40	6/7	62% (12)	15.2 (5.3)	
	0.50	6/6	82% (8)	15.9 (5.1)	
	1.00	9/9	99% (1)	11.5 (1.9)	0.33 mg/kg (0.24–0.47)
N-Et CAT	0.25	7/7	13% (5)	13.7 (2.9)	
	0.6	4/4	10% (6)	20.7 (6.3)	
	0.8	7/7	54% (7)	9.0 (2.6)	
	1.0	7/7	92% (4)	11.3 (2.7)	0.77 mg/kg (0.63–0.95)
N-Pr CAT	1.0	5/5	2% (1)	11.8 (2.9)	
	2.0	5/5	35% (13)	6.3 (1.7)	
	3.0	5/5	93% (3)	5.0 (0.8)	2.03 mg/kg (1.36–3.04)
(±)DiMe CAT	0.3	4/4	6% (6)	14.6 (5.0)	
	0.6	4/4	46% (19)	6.0 (1.6)	
	1.0	4/4	88% (9)	9.3 (3.9)	0.61 mg/kg (0.33–0.61)
(−)DiMe CAT	0.25	4/4	11% (4)	10.8 (3.7)	
	0.5	4/4	55% (5)	8.6 (2.6)	
	1.0	4/4	99% (1)	18.0 (7.1)	0.44 mg/kg (0.24–0.79)
(+)DiMe AMPH	1.0	4/4	4% (3)	14.9 (4.2)	
	3.0	4/4	42% (14)	10.6 (5.0)	
	5.0	4/4	88% (12)	8.1 (2.4)	
	10.0	3/4	100%	5.4 (1.5)	2.92 mg/kg (1.57–5.42)
MDC	1.5	3/4	12% (7)	11.6 (5.5)	
	2.5	8/9	32% (13)	7.4 (1.3)	
	2.75	7/9	58% (9)	5.5 (1.3)	
	2.85	5/9	50% (15)	4.8 (1.0)	
	3.0	3/9	—‡		
	3.0	3/9	—‡		
	3.5	0/5	—‡		
MDMC	1.0	4/4	2% (2)	17.1 (6.8)	
	2.0	5/5	26% (16)	7.1 (3.7)	
	2.5	4/5	29% (19)	7.5 (4.8)	
	2.75	4/5	69% (17)	3.8 (0.8)	
	3.0	4/4	90% (9)	3.7 (0.9)	2.36 mg/kg (1.83–3.06)
Saline (1 ml/kg)		9/9	2% (1)	16.2 (4.0)	

*n = Number of animals responding/number of animals to receive drug.

†Data obtained during a 2.5-min extinction session.

‡Disruption of behavior; majority of animals failed to make ≥5 responses during the entire 2.5-min extinction session. The 3.0 mg/kg dose was evaluated twice; in one case the three responding animals made 0, 75, and 90% of their responses on the drug-appropriate lever with response rates of 3.6, 3.2, and 4.0 responses/min, respectively, whereas in the second case, the three responding animals made 43, 0, and 80% of their responses in the same manner with response rates of 2.8, 4.8 and 8.0 responses/min, respectively.

just the pH to 9–10; the reaction mixture was extracted with chloroform (4 × 50 ml) and the solution was filtered through anhydrous sodium sulfate. The hydrochloride salt was formed by the addition of a solution of HCl gas in 2-propanol (4.5 N) and the reaction mixture was evaporated to dryness on a steam bath. The recovered solid was dissolved in hot 2-propanol followed by the careful addition of diethyl ether until turbidity was noted. The next day, after having been stored in a freezer overnight, the solution was filtered, and the crystalline material was collected and dried under vacuum for at least 2 days. The melting points (Hoover Unimelt apparatus) were found to be: N-Et CAT, mp 186–188°C (mp 183°C) (23), (mp 182°C) (26); N-Pr CAT, mp 180–182.5°C, (mp 180°C) (23), (mp 182°C) (26); Di Me CAT, mp 206–206.5°C (mp 202–204°C) (28). S(−)-N,N-Dimethylcathinone HCl, mp 197.5–200°C; (α) = −52.5 (H_2O, 1%), (mp 197–199°C; (α) = −52.5 (H_2O)) (32) was prepared from 1*R*,2*S*-*N*-methylephedrine HCl (Aldrich) by oxidation with sodium dichromate/sulfuric acid in a manner analogous to that previously described for the preparation of *S*(−)methcathinone HCl (18).

(±)3,4-Methylenedioxycathinone hydrochloride (MDC) was prepared from 3,4-methylenedioxypropiophenone (Frinton Laboratories, Vineland, NJ, recrystallized from isooctane to mp 40–41.5°C) in a series of steps. Isonitroso-3,4-methylenedioxypropiophenone (mp 149–151°C; literature mp 153–154°C (2)) was synthesized using the method described by Hartung et al. (20–22) for the synthesis of isonitrosopropiophenone by using butyl nitrite and substituting methylenedioxypropiophenone for propiophenone. The intermediate oxime was catalytically reduced using a low-pressure hydrogenation apparatus (Parr Instrument Co., Moline, IL): the oxime in acidic (HCl gas) ethanol was hydrogenated over a 2-h period with 10% palladium on carbon catalyst (20,24). Removal of the catalyst by filtration and evaporation of the solvent under reduced pressure gave MDC after recrystallization from 2-propanol-ether, mp 208–209°C. 3,4-Methylenedioxymethcathinone hydrochloride (MDMC) was prepared by brominating 3,4-methylenedioxypropiophenone using the method (option b) of Boyer and Straw (4) to give 2-bromo-3′, 4′-methylenedioxypropiophenone (mp 51–53°C). This compound in a mixture of absolute ethanol-diethyl ether (5:1) was added in a dropwise manner to an ice-cold 40% aqueous methylamine free base solution using the technique described above in the preparation of N-Et CAT. The recovered material was purified by dissolution in hot 2-propanol followed by precipitation upon the addition of diethyl ether to give the desired product, mp 226–228°C. All new compounds analyzed correctly (Atlantic Microlab) for C, H, and N to within 0.4% of theory, were homogeneous by gas–liquid chromatography, and structures were consistent with spectral data.

TABLE 2

RESULTS OF STIMULUS GENERALIZATION STUDIES WITH 3,4-METHYLENEDIOXYCATHINONE (MDC) AND *N*-METHYL-MDC (MDMC) IN RATS TRAINED TO DISCRIMINATE DOM (1.0 mg/kg) OR MDMA (1.5 mg/kg) FROM SALINE VEHICLE

	Dose (mg/kg)	*n**	%DOM-Appropriate Responding (±SEM)†	Responses/Minute (±SEM)†
		A. DOM-Trained Animals		
MDC	0.5	6/6	1% (1)	7.5 (1.4)
	1.5	4/6	2% (1)	6.8 (1.5)
	2.0	4/7	7% (4)	3.2 (0.7)
MDMC	1.0	7/7	2% (2)	7.8 (2.7)
	1.5	4/7	0%	5.3 (1.5)
	2.0	3/7	—‡	
DOM	1.0	7/7	98% (1)	6.9 (1.9)
Saline (0.9%)	1 ml/kg	7/7	4% (2)	8.6 (2.3)
	Dose	*n**	%MDMA-Appropriate Responding (±SEM)†	Responses/Minute (±SEM)
		B. MDMA-Trained Animals		
MDC	1.5	6/7	36% (20)	6.3 (1.8)
	2.0	7/8	77% (12)	6.6 (2.8)
	2.25	4/7	93% (7)	4.9 (0.3)
			ED_{50} = 1.64 (95%CL 1.37–1.97) mg/kg	
MDMC	1.5	4/8	33% (24)	6.1 (0.9)
	1.75	5/7	70% (16)	4.6 (1.0)
	2.0	5/7	98% (2)	6.2 (1.5)
			ED_{50} = 1.60 (95%CL 1.43–1.79) mg/kg	
MDMA	1.5	8/8	97% (1)	9.1 (2.3)
Saline (0.9%)	1.0 ml/kg	8/8	2% (1)	13.2 (4.8)

*Number of animals responding during the 2.5-min extinction session/number of animals receiving drug.

†Data obtained during the 2.5-min extinction session.

‡Disruption of behavior; majority of the animals failed to make ≥5 responses during the extinction session. For the three animals that did respond, their % DOM-appropriate responding (and responses per min): 0%(2.4), 0%(6.4), 0%(5.6).

RESULTS

N-Monoethylcathinone (N-Et CAT; ED_{50} = 0.77 mg/kg), *N*-mono-*n*-propylcathinone (N-Pr CAT; ED_{50} = 2.03 mg/kg), racemic *N*,*N*-dimethylcathinone and its (−)-isomer [(±)Di Me CAT, ED_{50} = 0.61 mg/kg; (−)Di Me CAT, ED_{50} = 0.44 mg/kg], and (+)*N*,*N*-dimethylamphetamine [(+)Di Me AMPH; ED_{50} = 2.92 mg/kg] all resulted in stimulus generalization when administered to (+)amphetamine-trained animals (ED_{50} = 0.33 mg/kg) (Table 1). In some cases [N-Pr CAT, (+)Di Me AMPH)], the animals' response rates were decreased to about 50% of control rates suggesting that the agents may possess some other rate-reducing action. 3,4-Methylenedioxymethcathinone (MDMC; ED_{50} = 2.36 mg/kg) also resulted in (+)amphetamine-stimulus generalization, whereas 3,4-methylenedioxycathinone (MDC) resulted only in a maximum of 58% (+) amphetamine-appropriate responding (Table 1). In both instances, response rates were reduced at the higher doses tested (Table 1); this may be related to the fact that both agents are capable of producing MDMA-like effects at these doses (see below). The latter two compounds were also examined in DOM-trained and MDMA-trained animals (Table 2). In the DOM-trained rats, neither compound elicited >7% DOM-appropriate responding at 1.5 mg/kg; at 2 mg/kg of MDC only four of seven animals made >5 responses during the extinction session whereas the same dose of MDMC disrupted the majority of animals tested. In the MDMA-trained animals (Table 2), both MDC and MDMC resulted in stimulus generalization (ED_{50} = 1.64 and 1.60 mg/kg, respectively). Where stimulus generalization occurred, the animals'response rates were decreased by 30–50%.

DISCUSSION

As appears to be the case with amphetamine (9,34,36,37), *N*-monomethylation of cathinone results (at least) in retention of potency (19), but any further increase in alkyl chain length results in a progressive decrease in potency (Table 1). The ED_{50} values for racemic cathinone, its *N*-methyl (i.e., methcathinone), N-ethyl (i.e., N-Et CAT), and *N*-*n*-propyl (i.e., N-Pr CAT) derivatives are 0.71, 0.37, 0.77, and 2.03 mg/kg) (see Table 3). These results, then, are not unexpected and represent parallels between amphetamine and cathinone structure–activity relationships. What was unexpected, however, is the potency of *N*,*N*-dimethylcathinone. (+)*N*,*N*-Dimethylamphetamine has previously been shown to be behaviorally active as a psychomotor stimulant in several animals species, and to result in stimulus generalization in animals trained to discriminate cocaine from vehicle (35). Conforming with its amphetamine-like activity, (+)*N*,*N*-dimethylamphetamine is also self-administered by squirrel monkeys (27). However, in all behavioral studies this agent was approximately 6–12 times less potent than (+)methamphetamine. Consistent with these observations, (+)*N*,*N*-dimethylamphetamine was found in the present investigation to be seven times less potent than (+)methamphetamine in producing (+)amphetamine-appropriate responding in rats trained to discriminate (+)amphetamine from vehicle (Tables 1 and 3). Interestingly, the corresponding cathinone analog, (±)Di Me CAT, was found to be only slightly (1.6-fold) less potent than racemic methcathinone (Tables 1 and 3). This represents the first divergence, albeit minor, between amphetamine structure–activity relationships and emerging cathinone structure–activity relationships and prompted us to examine what should be the more active optical isomer of Di Me CAT. The optically active (−)Di Me CAT was also only slightly (1.6-fold) less potent than its corresponding cathinone analog (i.e., (−)methcathinone) (see Tables 1 and 3). In fact, this agent was found to be at least as potent as its structural parent: (−)cathinone. It would appear, then, that here is a case where structure–activity relationships of amphetamine and cathinone appear to vary from a potency perspective.

TABLE 3

A COMPARISON OF THE POTENCIES OF AMPHETAMINE AND CATHINONE ANALOGS AS DETERMINED IN TESTS OF STIMULUS GENERALIZATION USING ANIMALS TRAINED TO DISCRIMINATE (+)AMPHETAMINE (1.0 mg/kg) FROM VEHICLE*

	ED_{50}, mg/kg (μmol/kg)		
Agent	Amphetamine Analogs	Cathinone Analogs	Agent
(+)Amphetamine	[0.33–0.45]†	0.42‡ (2.3)	(−)Cathinone
(±)Amphetamine	0.71§ (3.0)	0.71§ (3.8)	(±)Cathinone
(+)Methamphetamine	0.40‡ (2.2)	0.25¶ (1.3)	(−)Methcathinone
(±)Methamphetamine	0.49§ (2.6)	0.37¶ (1.9)	(±)Methcathinone
(+)N-Et amphetamine	0.87# (4.4)	0.77 (3.6)	N-Et CAT
	—	2.03 (8.9)	N-Pr CAT
	—	0.61 (3.0)	(±)Di Me CAT
(+)N,N-Di Me AMPH	2.92 (15.4)	0.44 (2.1)	(−)Di Me CAT
MDA	2.29‡ (11.2)	—**	MDC
MDMA	1.64‡ (7.5)	2.36 (10.1)	MDMC

*Data are from the present study except where noted; some of the ED_{50} values are from previous studies conducted in our laboratory and are included only for comparison. All agents represent racemates unless otherwise noted.

†Due to extensive work with 1 mg/kg of (+)amphetamine as a training drug, we have previously published ED_{50} values on a number of different occasions; these ED_{50} values have ranged from 0.33 (present study) to 0.45 mg/kg and for purpose of comparison we provide the entire range here.

‡Data from (8). §Data from (19). ¶Data from (18). #Data from (17). **Partial generalization (present study; see Table 1).

Will the cathinone molecule serve as phenylisopropylamine surrogate in the sense that structural modification might alter the nature of its actions in a manner that parallels those observed upon structural modification of amphetamine? That is, incorporation of a 3,4-methylenedioxy group converts amphetamine from a central stimulant to an agent (i.e., MDA) that now possesses a combination of central stimulant, DOM-like, and MDMA-like character. For example, stimulus generalization occurs with MDA both in (+)amphetamine-trained animals and in DOM-trained animals [see (39) for discussion]. Stimulus generalization with MDA also occurs in animals trained to discriminate MDMA from vehicle (10,29). Futhermore, with MDA as the training drug, stimulus generalization occurs to (+)amphetamine, DOM, and MDMA (14). Will the same structural modification of cathinone produce a similar consequence? Accordingly, we prepared MDC and its *N*-monomethyl derivative MDMC. Results with the methylenedioxy derivatives of cathinone are quite interesting. The cathinone counterpart, 3,4-methylenedioxycathinone or MDC, failed to completely substitute for (+)amphetamine or DOM (Tables 1 and 2). Thus, introduction of the carbonyl group has changed the properties of the molecule so that it no longer seems to function in the same manner as its parent (i.e., MDA). This represents a qualitative divergence in the structure–activity relationships of amphetamine and cathinone.

The *N*-monomethyl derivative of MDA, MDMA, possesses amphetamine-like character but lacks DOM-like properties (10). N-Monomethylation of MDC affords an agent, MDMC, that behaves in a similar fashion. That is, a (+)amphetamine stimulus (Table 1), but not a DOM stimulus (Table 2), generalized to MDMC. In terms of amphetamine-like activity, MDMC (ED_{50} = 10.1 μmol/kg) is similar in potency to MDMA (ED_{50} = 7.5 μmol/kg) (Table 3). In this instance then, the effect of introducing the carbonyl oxygen was simply to slightly reduce amphetamine-like potency.

From the foregoing discussion it would seem that MDC no longer behaves like MDA but that MDMC retains the amphetamine-like character of MDMA. Interestingly, both MDC and MDMC retain MDMA-like character (Table 2) in that they completely substituted for MDMA (i.e., they produced >80% MDMA-appropriate responding) in MDMA-trained rats. Because MDMC (ED_{50} = 1.6 mg/kg; 6.9 μmol/kg) was about half as potent as MDMA itself (ED_{50} = 0.76 mg/kg; 3.5 μmol/kg) (12), it would seem that here, too, the effect of carbonyl-oxygen introduction is to decrease potency.

It is fairly apparent that although certain structural modifications of cathinone result in agents that behave in the expected manner (e.g. methcathinone, N-Et CAT), there are other changes that result in stimulus effects (e.g., those of Di Me CAT, MDC) that do not necessarily parallel those seen upon the same modification of the phenylisopropylamine amphetamine. These differences are both quantitative (i.e., as reflected by altered potency) and/or qualititative (i.e., as reflected by different generalization profiles). Future investigations of cathinone analogs will require an examination of agents on a case-by-case basis, and extrapolation of amphetamine structure–activity relationships to cathinone analogs should be done cautiously. In any event, the variously substituted cathinone analogs clearly retain some amphetamine-like character and, as with MDC and MDMC, MDMA-like character. Due to the possibility that cathinone-related analogs may eventually appear on the clandestine market as novel designer drugs, further investigation of these interesting compounds is warranted. Reexamination of these same agents in animals trained to discriminate (−)cathinone from vehicle would also seem warranted to determine if similar results would be obtained.

ACKNOWLEDGEMENTS

This work was supported, in part, by NIH Grant DA-01642. We would like to thank Dr. M. Gabryszuk for his assistance with some of the stimulus generalization studies.

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