



0091-3057(94)00348-3

# Methcathinone ("Cat"): An Enantiomeric Potency Comparison

RICHARD A. GLENNON,<sup>\*1</sup> RICHARD YOUNG, BILLY R. MARTIN\*  
AND TERRY A. DAL CASON†

*Department of Medicinal Chemistry, School of Pharmacy, and \*Department of Pharmacology, Medical College of Virginia, Virginia Commonwealth University, Richmond, Virginia 23298-0540*  
†North Central Laboratory, Drug Enforcement Administration, 500 U.S. Customhouse, Chicago, IL 60607

Received 20 December 1993

GLENNON, R. A., R. YOUNG, B. R. MARTIN AND T. A. DAL CASON. *Methcathinone ("cat"): An enantiomeric potency comparison*. PHARMACOL BIOCHEM BEHAV 50(4) 601-606, 1995.—With regard to its chemical structure, methcathinone is to cathinone what methamphetamine is to amphetamine. Although it is a drug of abuse outside the United States, methcathinone is only recently making an appearance on the clandestine market in this country and has just been classified a Schedule I substance under the Emergency Scheduling Act. We have previously demonstrated that racemic methcathinone produces locomotor stimulation in mice, and substitutes for cocaine and (+)amphetamine in rats trained to discriminate either cocaine or (+)amphetamine, respectively, from saline in tests of stimulus generalization. Because an enantiomeric potency comparison has never been reported for the optical isomers of methcathinone, in the present investigation we synthesized samples of S(-) and R(+)methcathinone and compared them for their ability: a) to produce locomotor stimulation in mice, b) to elicit cocaine-like responding in rats trained to discriminate 8.0 mg/kg of cocaine from saline vehicle, and c) to elicit (+)amphetamine-appropriate responding in rats trained to discriminate 1.0 mg/kg of (+)amphetamine from saline vehicle. S(-)Methcathinone was about twice as potent as S(+)-amphetamine and three to five times more potent than R(+)methcathinone in the three pharmacologic assays. We conclude that both optical isomers possess central stimulant character, but that S(-)methcathinone is somewhat more potent than R(+)methcathinone.

Methcathinone    Amphetamine    Cocaine    Central stimulants    Drug discrimination    Optical isomers

KHAT (*Catha edulis*) is a shrub that has been used for centuries in parts of Africa and the Arabian peninsula for its central stimulant effects (19). Although several methods of consumption are known, chewing of fresh khat leaves is the most common (17). Early work in the 1930s identified (+)norpseudoephedrine [i.e., (+)cathine] as one of the active principles of khat [see (1)]. However, because (+)cathine is only a weak central stimulant, this did not seem to account fully for the central actions of khat. In the 1970's, cathinone (an oxidized form of cathine) was identified as a more likely, and more potent, centrally active constituent of khat (25). The 1930's studies were conducted with dried plant material, whereas the later studies employed fresh khat leaves. Thus, decomposition of cathinone to cathine might account for its lack of detection in aged plant samples. More recently, it has been demonstrated that cathinone is about eight times more potent than

(+)cathine in producing amphetamine-like stimulus effects in rats (9).

The discovery of cathinone triggered a relatively widescale pharmacologic investigation of this novel substance [see (15,17,28)]. Although not without controversy, it was generally regarded that cathinone is an amphetamine-like central stimulant. Contributing to the initial confusion was the fact that, although (+)amphetamine is more potent than (-)amphetamine, (-)cathinone is several times more potent than (+)cathinone in producing central stimulant effects [e.g., (9,10,13,14)]. However, (+)amphetamine and (-)cathinone share the same absolute stereochemistry (i.e., S)—that is, S(-)cathinone is more structurally similar to S(+)-amphetamine than it is to R(-)amphetamine (Fig. 1) (10). To show the similarity between amphetamine and cathinone, a) we examined and compared the pharmacology of cathinone and am-

<sup>1</sup> Address reprint requests to Dr. Richard A. Glennon, Department of Medicinal Chemistry, School of Pharmacy, Medical College of Virginia, Virginia Commonwealth University, Box 540, MCV Station, Richmond, VA 23298-0540.

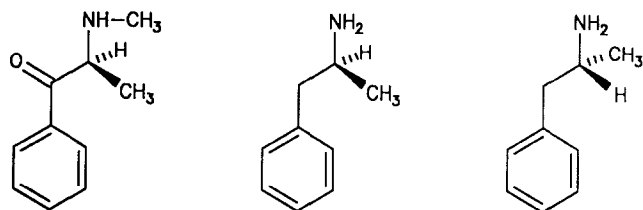


FIG. 1. Chemical structures of S(-)methcathinone, S(+)-amphetamine, and R(-)amphetamine (left to right), showing the greater structural similarity of S(-)methcathinone to the S(+)- rather than the R(-)-isomer of amphetamine.

phetamine, and b) we compared the effect of parallel structural modifications. For example, we demonstrated that, like amphetamine, cathinone could release stores of dopamine from rat caudate nucleus (18). It was also shown that cathinone and amphetamine produce similar stimulus effects regardless of which is used as the training drug [e.g., (9,31)], and that like amphetamine, stimulus generalization to cathinone is potently antagonized by haloperidol (18). In general, when two agents produce similar pharmacologic effects, parallel structural modification usually results in parallel changes in action and potency. Thus, we examined pairs of compounds to see whether this was the case for amphetamine and cathinone. Most structural modifications of amphetamine (e.g.,  $\alpha$ -demethylation, chain homologation, aromatic substitution) reduce or abolish its central stimulant actions (8). We demonstrated that  $\alpha$ -desmethylcathinone and various aromatic-substituted cathinone derivatives are significantly less potent than cathinone (10,18,31). One structural modification of amphetamine that does not reduce, and in fact enhances, potency is *N*-monomethylation. *N*-Monomethylamphetamine (methamphetamine) is at least twice as potent as amphetamine as a central stimulant (31). We reasoned that if cathinone is merely a naturally occurring amphetamine-like substance, its *N*-monomethyl derivative (which we termed "methcathinone") should at least retain the central stimulant potency of cathinone. It was thought that such a demonstration would aid in abating some of the confusion associated with cathinone. Indeed, methcathinone was found to be more potent than cathinone, both as a locomotor stimulant in mice and in tests of stimulus generalization using rats trained to discriminate (+)amphetamine from saline vehicle (11). Later studies demonstrated that methcathinone also produces cocaine-like stimulus effects (32).

Relatively little has been published on cathinone or methcathinone in the past half-dozen years. However, these agents are once again attracting attention. Within the past year or so, there has been an increased popular awareness of khat as a result of reports emanating from the conflict in Somalia. Also coming to light for the first time is the fact that methcathinone is a very significant drug-abuse problem in the former Soviet Union (3,24). Apparently, methcathinone, known in Russia as ephedrone or "jeff," "Jee cocktail," and "cosmos" (24), has been an abuse problem since at least the early 1980's; but no written accounts of methcathinone abuse had ever been published. Also, within the past year, methcathinone is appearing on the clandestine market in this country, and a number of underground methcathinone laboratories have been closed down by the Drug Enforcement Administration (J. Tolliver, personal communication). Methcathinone has been recently classified as a Schedule I substance (4). Some of the

confiscated methcathinone has been shown to be the racemate; however, some samples have been identified as S(-)methcathinone.

Chemically, methcathinone is 2-methylaminopropiophenone; it was first synthesized by the Germans (20,21,26) and the French (6) in the late 1920's as an intermediate in the synthesis of ephedrine. The optical isomers of methcathinone were first reported in 1936 (3), and the (-)-isomer was later patented as an analeptic (22,23). Although both the (-)- and (+)-isomers have been previously reported (3,23,27), there are no reports in the literature of an enantiomeric comparison of methcathinone isomers. Thus, we prepared samples of S(-)- and R(+)-methcathinone and examined these optical isomers for their ability to produce locomotor stimulation in mice and stimulus generalization in rats trained to discriminate either (+)amphetamine or cocaine from saline vehicle.

## METHODS

### Locomotor Studies

The locomotor studies used male albino ICR mice (20–25 g) obtained from Dominion Laboratories (Dublin, VA). The mice were maintained on a 12 L : 12 D cycle with free access to food and water. To measure spontaneous activity, mice were placed in individual photocell activity cages (6.5 × 11 in) consisting of 16 photocell beams per chamber. Individual mice were placed into one of six chambers and allowed to acclimate for 10 min. They were removed from the chambers and injected intraperitoneally (IP) with either saline or drug. Ten minutes after injection, the mice were returned to the chambers and interruptions of the photocell beams were recorded for the next 40 min using a Digiscan Animal Activity Monitor (Omnitech Electronics, Inc., Columbus, OH). Activity in the chamber was then expressed as the total number of beam interruptions for each 10-min period, as well as for the total 40-min session. Data are presented here only for the total 40-min session. The injection volume was 10 ml/kg. A minimum of six mice were used at each dose of each agent; no animal was used more than once. To calculate potency, the data were converted to percent of control and plotted vs. the log of the dose—that is, data were expressed as percent stimulation (percent of locomotor activity in the saline-treated group). Linear regression analysis was used to calculate a dose that produced a 300% response, which we term the effective dose 300 (ED<sub>300</sub>).

### Drug Discrimination Studies

The drug discrimination studies employed two groups of male Sprague-Dawley rats. One group ( $n = 6$ ) was trained to discriminate cocaine hydrochloride (8 mg/kg) from 0.9% saline vehicle, whereas the second group ( $n = 3$ ) was trained to discriminate (+)amphetamine sulfate (1.0 mg/kg) from saline, using a variable-interval, 15-s schedule of reinforcement for food (sweetened reconstituted powdered milk) reward. A detailed description of the methods employed in training the cocaine-trained animals was recently reported (32). Just before initiation of the present studies, two of the rats died. Thus, all data reflect the results of the responding of all four animals at all doses tested. The (+)amphetamine-trained animals were trained in a manner identical to that previously reported on several occasions (11,31). Standard two-lever operant chambers (model E10-10; Coulbourn Instruments, Allentown, PA) were housed within light- and sound-attenuating outer chambers. A dipper mechanism for the delivery of milk

was situated equidistant between the two levers, and the operant chamber was dimly illuminated by an overhead house light.

Animals were first trained to respond on one lever following saline administration, and then on the opposite lever following administration of training drug. For approximately half of the animals the right lever was designated the saline-appropriate lever, whereas the reverse was true for the remainder of the animals. During training, animals were administered training drug or saline on a double-alternation schedule 15 min before being placed in the operant chamber. The training sessions were 15 min per day. Training was assessed weekly by a 2.5-min extinction session followed by a 12.5-min training session. Once the animals made >80% of their responses during extinction sessions on the drug-correct lever following administration of the training dose of the training drug, and <20% of their responses on the same lever following administration of saline (1.0 ml/kg), for 3 consecutive weeks, they were employed in tests of stimulus generalization. In the generalization tests, doses of training drug would occasionally be replaced by doses of a test drug and the animals performance would be evaluated in a 2.5-min test session under extinction conditions. The animals would be immediately returned thereafter to their individual home cages. Response rates (responses

per minute) and responding (percent of total responses on the drug-designated lever) were recorded. When stimulus generalization (i.e., >80% drug-appropriate responding) occurred,  $ED_{50}$  values were calculated by the method of Finney (5). For purposes of comparison,  $ED_{50}$  values obtained in the cocaine-trained animals were compared with the  $ED_{50}$  value for cocaine itself; this latter value was obtained using all six animals (32). All solutions were prepared fresh daily using 0.9% sterile saline solution. Injection volumes were held constant at 1 ml/kg, and injections were made via the IP route.

**Drugs.** S(+)-Amphetamine sulfate and cocaine hydrochloride were purchased from Sigma (St. Louis, MO). The methcathinone isomers were prepared at the North Central Laboratory of the Drug Enforcement Administration following, essentially, the described patent procedure (23). A chilled ( $-5^{\circ}\text{C}$ ) solution of sodium dichromate in dilute sulfuric acid was added in a dropwise manner over 45 min to dilute sulfuric acid solutions of ephedrine (Aldrich, Milwaukee, WI) enantiomers at ice/salt-bath temperature. The reaction mixtures were washed with cold chloroform made basic with saturated sodium carbonate solution, extracted (four times) with chloroform, and dried with anhydrous sodium sulfate. The hydrochloride salt of each enantiomer was formed by addition of a solution HCl (g) in isopropanol (4.5 N) diluted 10-fold with

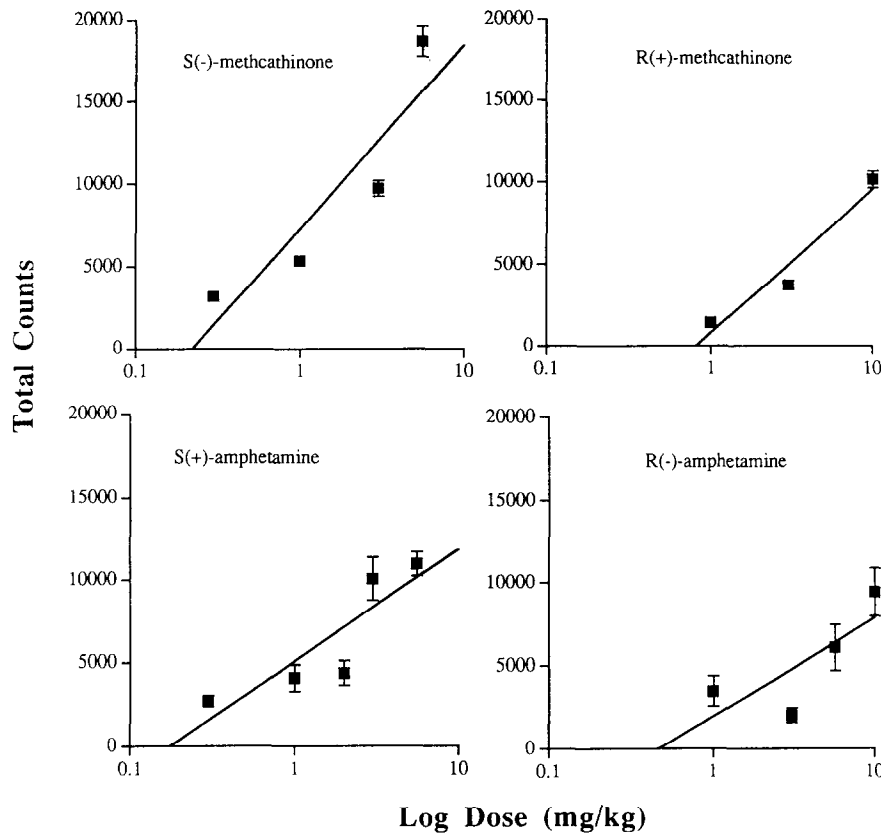


FIG. 2. Effects of methcathinone and amphetamine enantiomers on locomotor activity in mice. Total accumulations of photocell interruptions during a 40-min session are plotted against log dose. The results are expressed as means  $\pm$  SE for at least six mice per group. Where SE is not shown, it was smaller than the size of the symbol. The locomotor activity (mean  $\pm$  SE) in the saline-treated groups that were evaluated concurrently with the S(-)-methcathinone-, R(+)-methcathinone-, S(+)-amphetamine-, and R(-)-amphetamine-treated groups were:  $1679 \pm 465$ ,  $1529 \pm 431$ ,  $2621 \pm 357$ , and  $1980 \pm 291$ , respectively.

diethyl ether. Additional diethyl ether was added to produce turbidity, with subsequent precipitation of the hydrochloride salts. The enantiomers were collected by filtration and allowed to air dry. The physicochemical properties of S(-)methcathinone hydrochloride (mp = 176–177.5°C; optical rotation<sub>H<sub>2</sub>O/1%</sub> [α]<sub>D</sub><sup>25</sup> = -52.3°) were consistent with those reported in the previous literature (mp = 173–175°C; rotation<sub>H<sub>2</sub>O/5.3%</sub> = -50.3°) (27), (mp = 182–184°C; rotation<sub>H<sub>2</sub>O/1%</sub> = -53°) (22). Likewise, data for R(+)methcathinone hydrochloride (mp = 176–177.5°C; rotation<sub>H<sub>2</sub>O/1%</sub> = +52.2°) were consistent with literature data (mp = 174–176°C; rotation<sub>H<sub>2</sub>O/3.1%</sub> = +52.0°) (27). The methcathinone isomers were stored as their dry white crystalline hydrochloride salts. The spectroscopic properties of racemic methcathinone have been described in detail (33), and the present isomers exhibited similar spectroscopic properties.

## RESULTS

### Locomotor Stimulation

We previously demonstrated that racemic methcathinone is a locomotor stimulant in mice that is several times more potent than racemic cathinone (11). In the present investigation, the locomotor activity of the two individual methcathinone optical isomers was compared with that produced by the isomers of amphetamine (Fig. 2). Potency comparisons were made by calculating the dose of compound required to produce an amount of locomotor stimulation equivalent to three times that observed after administration of saline vehicle to the same animals (i.e., effective dose or ED<sub>300</sub>). S(-)Methcathinone (ED<sub>300</sub> = 0.6 mg/kg) was found to be several times more potent than R(+)methcathinone (ED<sub>300</sub> = 3.0 mg/kg), and more potent than either S(+)amphetamine or R(-)amphetamine (ED<sub>300</sub> = 2.6 and 4.7 mg/kg). On a molar basis, S(-)methcathinone (3.2 μmol/kg) is approximately 3.5 times more potent than S(+)amphetamine (11.2 μmoles/kg) and about six times more potent than R(-)amphetamine (20.3 μmol/kg). The potency of R(+)methcathinone (17.0 μmol/kg) falls between those of the two optical isomers of amphetamine.

### Stimulus Properties

We have previously shown that racemic methcathinone produces both cocaine-like (32) and amphetamine-like (11) stimulus effects in rats trained to discriminate cocaine and (+)amphetamine, respectively, from saline vehicle. In the present investigation, both isomers of methcathinone also substituted, in a dose-related manner, for cocaine in cocaine-trained animals (Fig. 3) and for S(+)amphetamine in S(+)amphetamine-trained animals (Fig. 4). In the cocaine-trained animals, S(-)methcathinone [ED<sub>50</sub> = 0.18 (95% CL = 0.10–0.32) mg/kg] was nearly three times more potent than R(+)methcathinone [ED<sub>50</sub> = 0.51 (95% CL = 0.29–0.90) mg/kg]. S(-)Methcathinone (ED<sub>50</sub> = 0.9 μmol/kg) was almost twice as potent as S(+)amphetamine [ED<sub>50</sub> = 0.34 (95% CL = 0.19–0.59) mg/kg, 1.5 μmol/kg] and more than eight times more potent than the training drug cocaine (ED<sub>50</sub> = 2.6 mg/kg; 7.6 μmol/kg) (32). The animals' response rates per minute after administration of S(-)methcathinone (9.8–14.5), R(+)methcathinone (10.3–12.8), and S(+)amphetamine (9.0–12.3) were similar to those recorded after administration of the training dose of cocaine (14.1 ± 2.0) or saline vehicle (12.9 ± 1.8). In S(+)amphetamine-trained animals (Fig. 4), S(-)methcathinone, ED<sub>50</sub> = 0.25 (95% CL = 0.10–

0.59) mg/kg or 1.3 μmol/kg, was nearly three times more potent than R(+)methcathinone, ED<sub>50</sub> = 0.66 (95% CL = 0.34–1.30) mg/kg or 3.3 μmol/kg, and somewhat more potent than S(+)amphetamine, ED<sub>50</sub> = 0.44 (95% CL = 0.20–0.99) mg/kg or 1.9 μmol/kg. Response rates per minute after the doses of methcathinone isomers (12.6–15.1) were not significantly different from those produced by the training dose of S(+)amphetamine (13.3 ± 1.8) or saline vehicle (13.1 ± 1.6). In every instance, all animals responded after administration of each dose of drug.

## DISCUSSION

Methcathinone has been a drug of abuse in the former Soviet Union for over a decade and is now making an appearance on the clandestine market in this country as "Cat." Although it may be considered a new "designer" drug, it was first synthesized more than 50 years ago. Its pharmacology has not been extensively documented. It produces significant locomotor stimulation in mice (11) and substitutes in (+)amphetamine- (11) and in cocaine-trained (32) animals. This finding, together with its ability to release stores of dopamine from rat caudate nucleus (11), suggests that it behaves as an amphetamine-like central stimulant. As with cathinone, it would be expected that S(-)methcathinone should be more potent than its R(+)-enantiomer. However, an enantiomeric comparison has never been reported. An early study showed that S(-)methcathinone was almost twice as potent as S(+)amphetamine as a "cerebral stimulant" (23); the R(+)isomer of methcathinone was not examined. In the present investigation we prepared samples of both methcathinone isomers for the purpose of enantiomeric comparison. In all three pharmacologic assays, S(-)methcathinone was more potent than R(+)methcathinone. As a locomotor stimulant in mice, S(-)methcathinone was five times more potent than its optical isomer. In drug discrimination studies using cocaine-trained rats, S(-)methcathinone (ED<sub>50</sub> = 0.18 mg/kg) was nearly three times more potent than R(+)methcathinone (ED<sub>50</sub> = 0.51 mg/kg), with the potency for racemic methcathinone (ED<sub>50</sub> = 0.39 mg/kg) falling between the potencies of

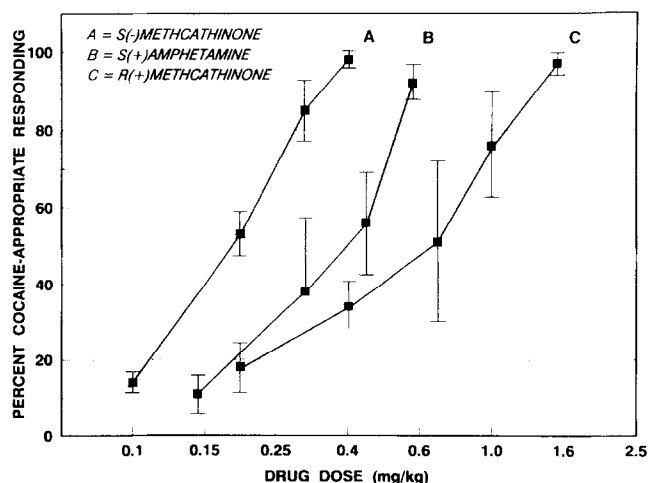


FIG. 3. The results of stimulus generalization studies using rats trained to discriminate cocaine from saline vehicle. Doses are provided on a per-milligram basis but are plotted on a log scale. Each animal ( $n = 4$ ) was used to examine each dose of every compound.

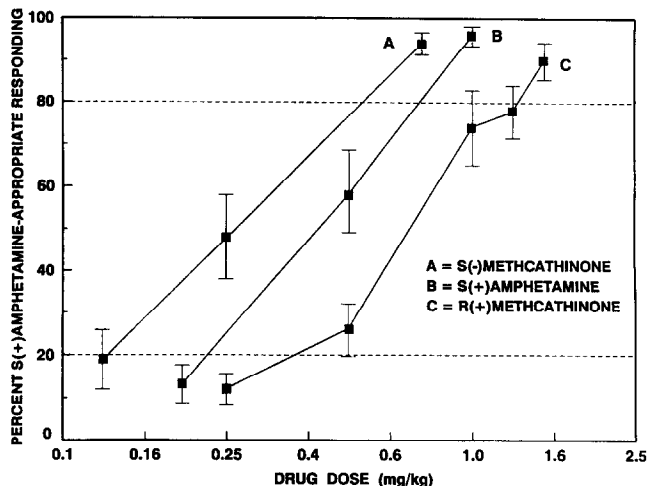


FIG. 4. The results of stimulus generalization studies using rats trained to discriminate S(+)-amphetamine from saline vehicle. Doses are provided on a per-milligram basis but are plotted on a log scale. Each animal ( $n = 3$ ) was used to examine each dose of every compound.

the two isomers. In the S(+)-amphetamine-trained animals, the S(-) isomer of methcathinone ( $ED_{50} = 0.25$  mg/kg) was more again potent than R(+)-methcathinone ( $ED_{50} = 0.66$  mg/kg); the potency of racemic methcathinone has been previously reported ( $ED_{50} = 0.37$  mg/kg) (11). Both in cocaine-trained and in S(+)-amphetamine-trained animals, S(-)-methcathinone was more potent than S(+)-amphetamine ( $ED_{50} = 0.33$  and  $0.44$  mg/kg, respectively). All of these results support the hypothesis that the S(-)-isomer is the more active isomer of methcathinone.

Chronic administration to humans of relatively high doses of amphetamine-like central stimulants can result in symptoms reminiscent of acute paranoid psychosis (i.e., "amphetamine psychosis") (2). Although khat-induced schizophreniform psychoses have been reported [e.g. (7,12)], cases are relatively infrequent, perhaps because of the sheer bulk of

crude plant product that would need to be ingested (16). However, with the availability of pure cathinone or methcathinone, "(meth)cathinone psychosis" may become a potential problem. Thus, it is important to have some understanding of these agents and to realize that they are, in many assays, quite amphetamine-like, but with a greater potency than amphetamine.

In the former Soviet Union, solutions of crude methcathinone (obtained directly from home synthesis) are typically administered by injection (24). In this country, several routes of administration have been seen, but nasal inhalation of methcathinone powder seems to be the preferred route (3). Because the present studies employed an IP route of administration, and because the metabolism of methcathinone has not been extensively investigated [see, however, (29)], the enantiomeric potency ratio may be somewhat different in humans. Nevertheless, because amphetamine-like central stimulants typically increase locomotor activity of mice (31) and result in stimulus generalization in both cocaine-trained (30) and amphetamine-trained (31) animals, we conclude that a) methcathinone possesses amphetamine-like central stimulant properties, b) methcathinone is somewhat more potent than amphetamine in this regard, c) methcathinone is more potent than cocaine, and d) S(-)-methcathinone is several times more potent than its R(+)-enantiomer.

The chewing of coca leaves has been, and continues to be, practiced by South American Indians. It was not until the active constituent (i.e., cocaine) was isolated and the route of administration altered that cocaine became a significant drug abuse problem. Likewise, there is a long history of khat chewing. Cathinone has been identified as the active stimulant constituent of khat, and methcathinone has been identified as a more potent central stimulant than cathinone (11). The preferred route of administration of methcathinone is not via the oral route. Thus, there are some parallels between these plant-related products as regards their abuse potential; further investigation of cathinone and methcathinone would appear to be warranted.

#### ACKNOWLEDGEMENTS

This work was supported in part by U.S. Public Health Service Grants DA-01642 (R.A.G.) and DA-02396 (B.R.M.).

#### REFERENCES

- Alles, G. A.; Fairchild, M. D.; Jensen, M. Chemical pharmacology of *Catha edulis*. *J. Med. Chem.* 3:323-352; 1961.
- Angrist, B. Psychoses induced by central nervous system stimulants and related drugs. In: Creese, ed. *Stimulants: Neurochemical, behavioral, and clinical perspectives*, I. New York: Raven Press; 1983:1-30.
- Bockmuhl, M. and Gorr, G. Verfahren zur Darstellung von optisch aktiven 1-aryl-2-amino-1-propanolen. German patent 639,126, 28 November, 1936.
- Bonner, R. C. Schedules of controlled substances temporary placement of methcathinone into Schedule I. *Fed. Reg.* 57:18824-18825; 1992.
- Finney, D. *Probit analysis*. London: Cambridge University Press; 1952.
- Fourneal, E. Procédé de préparation du phenyl-méthyl-amino-propanol (ephedrine synthétique). French patent 659,882, 4 July, 1929.
- Giannini, A. J.; Castellani, S. A manic-like psychosis due to khat (*Catha edulis*). *J. Toxicol. Clin. Toxicol.* 19:455-459; 1982.
- Glennon, R. A. Psychoactive phenylisopropylamines. In: Meltzer, H., ed. *Psychopharmacology: Third generation of progress*. New York: Raven Press; 1987:1627-1634.
- Glennon, R. A.; Schechter, M.; Rosecrans, J. A. Discriminative stimulus properties of S(-) and R(+)-cathinone, (+)-cathine and several structural modifications. *Pharmacol. Biochem. Behav.* 21:1-3; 1984.
- Glennon, R. A.; Showalter, D. The effect of cathinone and several related substances on locomotor activity. *Res. Commun. Subst. Abuse* 2:186-192; 1981.
- Glennon, R. A.; Yousif, M.; Naiman, N.; Kalix, P. Methcathinone: A new and potent amphetamine-like agent. *Pharmacol. Biochem. Behav.* 26:547-551; 1987.
- Gough, S. P.; Cookson, I. B. Khat-induced schizophreniform psychosis in UK. *Lancet* 455; 1984.
- Johanson, C. E.; Schuster, C. R. A comparison of the behavioral effects of l and dl-cathinone and d-amphetamine. *J. Pharmacol. Exp. Ther.* 219:355-362; 1981.
- Kalix, P. Hypermotility of the amphetamine type induced by a constituent of khat leaves. *Br. J. Pharmacol.* 68:11-13; 1980.

15. Kalix, P. The pharmacology of khat. *Gen. Pharmacol.* 15:179-187; 1984.
16. Kalix, P. Amphetamine psychosis due to khat leaves. *Lancet* 46; 1984.
17. Kalix, P.; Braenden, O. Pharmacological aspects of the chewing of khat leaves. *Pharmacol. Rev.* 37:149-164; 1985.
18. Kalix, P.; Glennon, R. A. Further evidence for an amphetamine-like mechanism of action of the alkaloid cathinone. *Biochem. Pharmacol.* 35:3015-3019; 1986.
19. Kennedy, J. G.; Teague, J.; Fairbanks, L. Qat use in North Yemen and the problem of addiction: A study in medical anthropology. *Cult. Med. Psychiatry* 4:311-344; 1980.
20. Knoll, A. G. Arylamino ketones. German patent 634,002, 14 August, 1936 (*Chem. Abstr.* 31:1821; 1937).
21. Merck Chemische Fabrik, Verfahren zur Darstellung von 1-phenyl-2-methylpropanol-1, German patent 472,466, 28 February, 1929.
22. L'Italien, Y. L.; Park, H.; Rebstock, H. B. Methylaminopropiophenone compounds and methods for preparing the same. U.S. patent 2,802,865, 13 August, 1957.
23. Parke, Davis, and Co. Aminoketones. British patent 768,772, 20 February, 1957 (*Chem. Abstr.* 51:15552; 1957).
24. Savenka, V. G.; Semkin, E. P.; Sorokin, V. I.; Kazonov, S. P. Expert examination of narcotic substances obtained from ephedrine. In: *Balamikha: All-Union Scientific Research Institute of Polygraphy*; 1989.
25. Schorno, X; Steinegger, E. CNS-Active phenylpropylamines of *Catha edulis* Forsk. (Celastraceae) of Kenyan origin. *Experientia* 35:572-574; 1979.
26. Stolz, F. Verfahren zur Darstellung von  $\alpha$ -methylaminopropiophenon. German patent 468,305, 10 November, 1928.
27. Takamatsu, M. Studies on optically active phenylpropanolamine derivatives. I. Preparation of optically active  $\alpha$ -aminopropiophenones by asymmetric transformation. *J. Pharm. Soc. Japan* 76: 1219-1222; 1956.
28. United Nations Bulletin on Narcotics. Volume XXXII(3); 1980. Special issue devoted to *Catha edulis*.
29. Vree, T. B.; Muskens, A. T. J. M.; Van Rossum, J. M. Metabolism of N-alkyl substituted aminopropiophenones in man in comparison to amphetamines and ephedrines. *Arch. Int. Pharmacodyn.* 197:392-395; 1972.
30. Woolverton, W. L. Discriminative stimulus effects of cocaine. In: Glennon, R. A.; Jarbe, T. U. C.; Frankenheim, J., eds. *Drug discrimination: Applications in drug abuse research*. Washington, DC: U.S. Government Printing Office; 1991:60-74.
31. Young, R.; Glennon, R. A. Discriminative stimulus properties of amphetamine and structurally related phenalkylamines. *Med. Res. Rev.* 6:99-130; 1986.
32. Young, R.; Glennon, R. A. Cocaine-stimulus generalization to two new designer drugs: Methcathinone and 4-methylaminorex. *Pharmacol. Biochem. Behav.* 45:229-231; 1993.
33. Zhingel, K. Y.; Dovensky, W.; Crossman, A.; Allen, A. Ephedrone: 2-Methylamino-1-phenylpropan-1-one (Jeff). *J. Forensic Sci.* 915-920; 1991.