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RAPID COMMUNICATION

Cocaine-Stimulus Generalization to Two New Designer Drugs: Methcathinone and 4-Methylaminorex

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YOUNG, R. AND R. A. GLENNON. *Cocaine-stimulus generalization to two new designer drugs: Methcathinone and 4-methylaminorex.* PHARMACOL BIOCHEM BEHAV 45(1) 229–231, 1993.—Rats were trained to discriminate 8 mg/kg cocaine from saline vehicle for the purpose of examining the stimulus properties of two novel and structurally related drugs of abuse recently confiscated on the illicit market: (±)methcathinone and *cis*(±)4-methylaminorex. The stimulus properties of these controlled substance analogs were compared with those of their parent compounds (±)cathinone and aminorex, respectively. All agents resulted in cocaine-stimulus generalization with the following rank order of potency: aminorex (ED_{50} value = 0.8 μM/kg) > methcathinone (1.9 μM/kg) > cathinone (3.7 μM/kg) > 4-methylaminorex (5.2 μM/kg) > cocaine (7.6 μM/kg).

Cocaine Cathinone Methcathinone Aminorex 4-Methylaminorex

SEVERAL controlled substance analogs (i.e., "designer drugs") are being, or recently have been, placed in Schedule I of the Controlled Substances Act. Interestingly, four of these agents that have been encountered on the clandestine market are not truly designer drugs; one (i.e., cathinone) is the active constituent of a shrub (khat; *Catha edulis*) that has been abused for several centuries, and the remainder (aminorex, 4-methylaminorex, and the *N*-methyl derivative of cathinone) were originally developed as potential anorectic agents by the pharmaceutical industry. However, their recent illicit appearance probably justifies this designation. These agents are structurally related to amphetamine in that they are phenylisopropylamine derivatives; they are all further related to one another, but are distinct from amphetamine, in possessing a benzylic oxygen function.

Not all phenylisopropylamines (e.g., fenfluramine) possess amphetamine-like central stimulant character (6); however, we previously reported that all four agents produce amphetamine-like effects. Additional background information on aminorex (11), 4-methylaminorex ("U4Euh"; 4-MAX) (7), and cathinone (5,6,8) may be found in these earlier reports. 2-Methylamino-1-phenylpropan-1-one was originally synthesized in 1936 (4); we resynthesized this agent several years ago to complete a structure-activity relationship (SAR) investigation and verify, on the basis of our SAR studies, that it would act as a central stimulant (i.e., structurally, this agent is to cathinone what methamphetamine is to amphetamine) (9). Due to its actions and greater potency in various pharmacological assays relative to cathinone, we coined the term methcathinone (9). This agent has now appeared on the clandestine market as "CAT" (1). Interestingly, it has recently come to light that methcathinone, under the name of ephedrone ("JEFF"), has seen widespread abuse in the former Soviet Union but that reports of its abuse had been suppressed [(2) and J. Tolliver, personal communication]. Methcathinone has now been temporarily scheduled under the emergency scheduling provisions of the Controlled Substances Act (2).

In the present study, we compare the ability of methcathinone and *cis*(±)4-methylaminorex to produce cocaine-like stimulus effects relative to their parent compounds: (±)cathinone and (±)aminorex.

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TABLE 1
RESULTS OF STIMULUS GENERALIZATION STUDIES WITH COCAINE-TRAINED ANIMALS

Agent	Dose (mg/kg)	n*	Cocaine-Appropriate Responding† (%)	Response Rate† (responses/min)
Cocaine HCl	1.0	6/6	10 (3)	14.2 (1.7)
	2.0	6/6	38 (11)	13.9 (2.0)
	4.0	6/6	72 (9)	15.1 (1.9)
	6.0	6/6	85 (9)	14.1 (1.7)
	8.0	6/6	97 (3)	14.8 (1.7)
	ED_{50} = 2.60 (1.43–4.55) mg/kg			
Saline (1 ml/kg)		6/6	7 (2)	13.1 (1.8)
(±)Cathinone	0.1	5/5	0	15.2 (1.6)
	0.25	5/5	4 (1)	13.9 (1.9)
	0.75	5/5	53 (17)	14.9 (2.1)
	1.5	5/5	93 (7)	9.2 (2.1)
	ED_{50} = 0.69 (0.34–1.39) mg/kg			
(±)Methcathinone	0.25	5/5	19 (4)	13.7 (1.6)
	0.50	5/5	58 (14)	14.2 (1.9)
	0.75	5/5	97 (1)	14.9 (1.7)
	ED_{50} = 0.39 (0.23–0.67) mg/kg			
(±)Aminorex	0.10	5/5	25 (4)	13.8 (1.6)
	0.25	5/5	43 (18)	14.5 (1.7)
	0.50	5/5	75 (17)	15.2 (1.3)
	0.75	5/5	96 (2)	13.7 (2.1)
	ED_{50} = 0.22 (0.12–0.43) mg/kg			
cis(±)4-MAX	0.5	5/5	8 (3)	13.5 (1.7)
	1.0	5/5	33 (9)	13.3 (2.1)
	1.5	5/5	72 (14)	12.6 (1.9)
	2.0	5/5	90 (4)	11.3 (1.2)
	ED_{50} = 1.11 (0.70–1.76) mg/kg			

*Number rats of responding/number treated.
†Data collected during 2.5-min extinction session.

METHOD

Subjects were 6 male Sprague-Dawley rats weighing 250–300 g at the start of the study. Animals were first trained to lever-press for sweetened milk reward using standard two-lever operant chambers (Coulbourn Instruments Model E10-10) housed within sound- and light-attenuating outer chambers. 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; 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 animals were returned to their home cages. During generalization tests, rats were injected with doses of a test compound 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. Where stimulus generalization occurred, ED_{50} values (i.e., doses at which animals would be expected to make 50% of their responses on the cocaine-appropriate lever) were calculated by the method of Finney (3).

Drugs

Racemic cathinone HCl was a gift from the World Health Organization and *cis*(±)4-methylaminorex HCl was a gift from the Drug Enforcement Administration. Methcathinone HCl was synthesized in our laboratories (9) and (±)aminorex fumarate was a gift from McNeil Labs (Fort Washington, PA). Cocaine HCl was purchased from Sigma Chemical Co. (St. Louis, MO). All solutions were prepared fresh daily and all agents were administered via IP injection in a 1.0-ml/kg injection volume.

RESULTS AND DISCUSSION

Cocaine has been employed in numerous drug discrimination studies and many central stimulants, including cathinone, substitute for the cocaine stimulus [reviewed in: (10)]. In the present investigation, rats were trained to discriminate 8 mg/kg (ED_{50} = 2.6 mg/kg; 7.6 μM/kg) cocaine from saline vehicle. Saline produced 7% drug-appropriate responding (Table 1). The cocaine stimulus generalized both to methcathinone and 4-methylaminorex in a dose-related fashion. Response rates for all doses of test compounds were comparable to that for cocaine (or saline) control rates.

Methcathinone (ED_{50} = 0.39 mg/kg; 1.9 μM/kg) was found to be nearly twice as potent as cathinone (ED_{50} = 0.69 mg/kg; 3.7 μM/kg); 4-methylaminorex (4-MAX; ED_{50} = 1.11 mg/kg; 5.2 μM/kg) is about six times less potent than aminorex (ED_{50} = 0.22 mg/kg; 0.8 μM/kg) (Table 1). Nevertheless, all four agents seem to possess cocaine-like stimulus character, with the order of potency being: aminorex > (±)methcathinone > (±)cathinone > *cis*(±)4-methylaminorex > cocaine.

Although phenylisopropylamines bearing a benzylic oxygen function are generally only weakly active when the oxygen function is a hydroxyl group (e.g., ephedrine, norpseudoephedrine), phenylisopropylamines with a benzylic oxygen in the form of a ketone (e.g., cathinone) or as part of a ring system (e.g., aminorex) are substantially more potent (6). The present results support and extend the results of our earlier studies and demonstrate that these benzylic oxygen-containing phenylisopropylamines can produce cocaine-like stimulus effects in animals.

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