Pergamon

Pharmacology Biochemistry and Behavior, Vol. 47, No. 4, pp. 981–983, 1994

0091-3057/94 $6.00 + .00

Intravenous Self-Injection of Methcathinone in the Baboon

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Received 19 July 1993

KAMINSKI, B. J. AND R. R. GRIFFITHS. *Intravenous self-injection of methcathinone in the baboon.* PHARMACOL BIOCHEM BEHAV 47(4) 981–983, 1994.—Methcathinone is a phenylisopropylamine that has been produced by clandestine laboratories and identified in illicit drug traffic. The present study evaluated the intravenous self-administration of methcathinone in three baboons using a cocaine substitution procedure. Intravenous self-injections were available 24 h/day according to a fixed-ratio (FR) schedule with a 3-h timeout following each injection. Doses of racemic methcathinone HCl (0.01–1.0 mg/kg/injection) and its vehicle were substituted for cocaine for 15 or more days. A concurrent FR schedule of food pellet delivery allowed evaluation of any changes in food intake. Self-injection of methcathinone was dose dependent. The lower doses of methcathinone, 0.01 and 0.032, maintained low and intermediate rates of self-injection, respectively, while the higher doses, 0.1, 0.32, and 1.0, maintained rates above vehicle control and comparable to those maintained by cocaine. Acute administration of 3.2 mg/kg to two baboons produced signs of psychomotor stimulant toxicity. Systematic changes in food intake were not observed. The present data indicate that methcathinone functions as a positive reinforcer in baboons and suggests that methcathinone may have abuse potential.

Methcathinone Cocaine Drug self-administration Psychomotor stimulants Baboons

METHCATHINONE (2-methylamino-1-phenylpropan-1-one) is the *N*-monomethyl analog of the phenylisopropylamine derivative cathinone (1). It has recently appeared in illicit drug traffic in the United States as CAT, and over 80 total encounters with the drug have been reported by law enforcement officials, including more than 25 clandestine laboratories seizures (12). As a result, in 1993, methcathinone was placed in Schedule I (for drugs with high abuse potential and no recognized therapeutic usefulness). Further, it has recently been revealed that methcathinone has been intravenously self-administered by drug abusers in Russia where it is known as ephedrone (16).

Structurally, both cathinone and methcathinone are similar to amphetamine. Cathinone and amphetamine differ only in that the two hydrogens on the β carbon of the amphetamine side chain are substituted by oxygen in cathinone. Cathinone has been self-administered by humans for centuries in the form of Khat leaf chewing (9) and has been reported to function as a positive reinforcer in intravenous self-administration experiments using rhesus monkeys (11,13,14). The reinforcing effects of methcathinone, however, have not been characterized. The present study evaluated the intravenous self-injection of methcathinone in the baboon using a cocaine substitution procedure that has been successfully used to evaluate of a wide range of phenylethylamine anorectics and other psychomotor stimulant compounds [e.g., (2,3,5,6,8,10).]

METHOD

Subjects

Three adult male baboons (*Papio cynocephalus* of the *cynocephalus* subtype; Primate Imports, New York, NY) were surgically prepared with chronically indwelling silastic catheters implanted in either femoral or jugular veins (7). The baboons had previously served in studies of intravenous (IV) self-injection with a variety of drugs [e.g., (4)]. The baboons had 24 h/day access to water and to food pellets (as described below). In addition, the baboons received one or two pieces of fresh produce and a multivitamin daily.

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Apparatus

Baboons were housed individually in standard stainless steel primate cages with an aluminum work panel mounted on the rear wall [for further details see (4)]. A Lindsley lever (Gerbrands, No. G6310), a vertically operated lever, a food hopper, jewel lights, and a Plexiglas panel that could be transilluminated were mounted on the panel. A speaker for delivery of tones and white noise was mounted behind the panel.

The IV catheters were protected by a tether/harness system that allowed virtually unrestricted movement within the cage (7). The catheter was attached to a valve system that allowed fluid delivery from three separate sources. One peristaltic pump continuously administered heparinized (5 units/ml) saline (125 ml/day) to maintain catheter patency. Drug was injected into the valve system by means of a second pump and then flushed into the animal with saline via a third pump [for further details see (4)].

Experimental control and data collection were accomplished using IBM-compatible microcomputers and related interfaces (MED Associates, Burlington, VT) with programs written in the MedState Notation Language® (MED Associates, Burlington, VT). Temporal patterning of responses was recorded using cumulative recorders (Gerbrands Corp., Arlington, MA).

Procedure

The general procedure has been described in greater detail elsewhere [e.g., (4)]. Briefly, drug injections were available by responding on the Lindsley lever under a fixed-ratio 160-response (FR 160; Baboons AC, VA) or 80-response (FR 80; Baboon PE) reinforcement schedule (i.e., completion of the response requirement produced a 5-ml drug or vehicle injection). Each injection was followed by a 3-h timeout, allowing a maximum of eight injections per day. Self-injection was established using cocaine reinforcement (0.32 mg/kg/injection). When the number of cocaine self-injections was six or more per day for 3 consecutive days (defined as criterion performance), a dose of racemic methcathinone (0.01–1.0 mg/kg/injection) or its vehicle was substituted for cocaine for a minimum of 15 days. Then, cocaine self-injection performance was reestablished; and when criterion performance was obtained, another dose of methcathinone or vehicle was substituted. Cocaine HCl (NIDA RTI, Research Triangle Park, NC) and racemic methcathinone HCl (Aldrich Chemical Company) were dissolved in 0.9% NaCl. Doses of cocaine and methcathinone are expressed as the salt.

Food pellets (1 g banana-flavored, Bio-Serv, Frenchtown, NJ) were available 24 h/day by responding on the vertically operated lever under an FR 30 reinforcement schedule. Data were recorded between 0800 and 1000 h daily and drug changes were performed during that time, if appropriate.

RESULTS

Figure 1 shows the mean number of injections per day for the last 5 days of vehicle or methcathinone (mg/kg/injection) availability and the grand mean of the 3 days of cocaine availability that preceded each substitution of a drug dose or vehicle. Cocaine maintained high rates of self-injection, typically seven or eight injections per day. In contrast, vehicle maintained low rates of self-injection. Self-injection of methcathinone was dose dependent. The lower doses of methcathinone (0.01 and 0.032 mg/kg/injection) maintained low and intermediate rates of self-injection, respectively. Higher doses of methcathinone (0.1, 0.32, and 1.0 mg/kg/injection) maintained rates of self-injection above vehicle control and comparable to those maintained by cocaine.

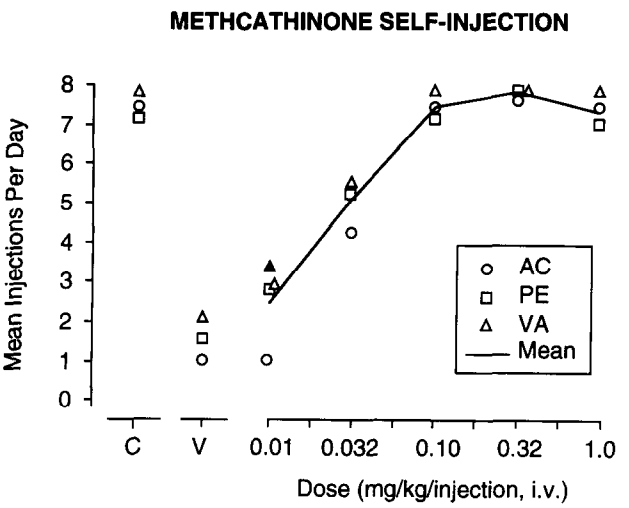

FIG. 1. Mean number of injections per day for the last 5 days of racemic methcathinone (mg/kg/injection) substitution under a fixed-ratio 160-response (or 80-response; Baboon PE) time-out 3-h schedule of intravenous injection. Individual data for three baboons are presented; different symbols designate different baboons. The vertical axis shows mean number of injections per day; the horizontal axis shows the doses of methcathinone (log scale). Data points above C indicate means of all 3-day periods of cocaine HCl (0.32 mg/kg/injection) availability that immediately preceded every substitution of a drug dose or vehicle. Data points above V indicate means of the last 5 days after substitution of the drug vehicle. Drug data points indicate mean of the last 5 days of substitution of a drug dose. The filled triangle shows a replication of the 0.01 mg/kg/injection dose substitution for Baboon VA. The line connects the grand mean at each dose.

During self-injection of cocaine, vehicle, and low doses of methcathinone, no unusual changes in the gross behavior of the baboons were observed. However, substitution of 1.0 mg/kg/injection methcathinone produced behavioral stimulation in two baboons (AC, VA; data not shown). In addition, acute administration of 3.2 mg/kg methcathinone to two baboons (PE, VA) produced signs of psychomotor stimulant toxicity that included stereotypic movements, behavioral agitation, tremors, and tracking of nonexistent visual objects (suggesting hallucinations). Finally, although there was a tendency for pellet intake to be suppressed during the first few days of substitution of high doses (0.32 and 1.0 mg/kg/injection), consistent changes in food intake were not observed.

DISCUSSION

In the present study, methcathinone maintained rates of intravenous self-injection above vehicle control and, at some doses (0.1, 0.32, and 1.0 mg/kg/injection), at rates comparable to those maintained by cocaine. These results indicate that methcathinone functioned as a positive reinforcer under the present conditions and are consistent with the growing number of DEA encounters with methcathinone.

The present results are similar to ones obtained previously under the same experimental parameters for the commonly abused stimulants amphetamine (5) and MDMA (6). However, unlike these other self-injected psychomotor stimulants, a cyclic pattern of self-injection (i.e., days on which high num-

bers of injections taken were interspersed with days on which low numbers of injections were taken) was not observed at doses of methcathinone that maintained maximal self-injection. It is possible that substitution of higher doses (e.g., 3.2 mg/kg/injection) or different availability parameters, may result in the cyclic pattern.

The present results are also consistent with the results of previous studies reporting that methcathinone has psychomotor stimulant properties. Methcathinone has been reported to be a locomotor stimulant (1) and to occasion amphetamine-lever responding (1) and cocaine-lever responding (15) in drug discrimination studies with rats. In the present study, acute administration of a high dose of methcathinone (3.2 mg/kg/injection) produced several gross behavioral effects (visual tracking, agitation, stereotypy, tremor) consistent with psychomotor stimulant toxicity and that have been observed in baboons following administration of high doses of amphetamine (10) and MDMA (6).

In summary, the behavioral pharmacology profile of methcathinone is like that of the abused psychomotor stimulants in that a) it maintains intravenous self-injection at rates above vehicle control; b) it produces discriminative stimulus effects similar to amphetamine and cocaine; and c) acute administration of high doses produces effects consistent with psychomotor stimulant toxicity. Taken together, these data suggest that methcathinone may have abuse liability comparable to that of other abused psychomotor stimulants.

ACKNOWLEDGEMENTS

Thanks to S. Womack, M. Turner, and J. Thomas for their technical assistance in conducting this study and Dr. James Tolliver for helpful discussions. Methcathinone was supplied by the Drug Enforcement Administration. This research and manuscript preparation was supported by National Institute on Drug Abuse Contract No. 271-86-8113 and Grant DA 01147.

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