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RELATIVE POTENCIES OF TWO PHENYLALKYLAMINES FOUND IN THE ABUSED PLANT CATHA EDULIS, KHAT

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Summary

Cathinone and d-norpseudoephedrine are closely related phenylalkylamines isolated from Catha edulis (khat), a plant much abused for its stimulant properties. We have compared the potency of these two compounds on an operant behavioral procedure in rats. Both suppress fixed ratio 20 responding for food in a dose related manner. Cathinone was 7-10 times more potent and had a more rapid onset of action than d-norpseudoephedrine, although the duration of action of cathinone was shorter. The ability of these two compounds to produce amphetamine-like stereotyped movements was in concordance with this same relative potency and difference in duration of action. Comparison of the behavioral effects in rats with the pattern of stimulation reported for khat use by man suggests that cathinone may be the major CNS active component of Catha edulis.

The CNS stimulant, d-norpseudoephedrine, was isolated from Catha edulis in 1930 (1). The fresh shoots and leaves of Catha edulis, called khat, are used in parts of Africa and the Middle East to combat mental fatigue, allay hunger and to induce euphoria (2). Some researchers have argued that the amount of d-norpseudoephedrine in Catha material is not adequate to account for the observed CNS effects (3,4). This argument has prompted research in an attempt to identify other pharmacologically active compounds in Catha. So far, several compounds have been isolated, but particular interest was given to a second phenylalkylamine, designated cathinone, the ketone congener of norpseudoephedrine.

The relative potency of d-norpseudoephedrine to chemically similar stimulants is known (5), but similar data is not available for cathinone. We have compared these compounds on an operant behavioral measure, a fixed ratio 20 (FR 20) schedule of food reinforcement. This behavior has been shown to be a sensitive and easily quanitified measure of the potency of similar stimulant drugs (6).

Methods

Six male Sprague-Dawley rats (Holtzman, Madison, Wisc.) were housed individually in a temperature and humidity controlled room on a 12 hour light-dark

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cycle. The rats were maintained at 80% of their normal body weights and had a three week history of responding on a FR 20 operant behavioral schedule of food reinforcement prior to this study. All behavioral sessions were conducted in standard operant chambers, with recording of lever responses and delivery of food pellets (P. J. Noyes Co., Lancaster, N.H.) controlled by a Nova-2 minicomputor (Data General Corp., Southboro, Mass.) through Interact interfacing (BRS/LVE, Beltsville, Md.). The operant behavior chambers were enclosed in sound attenuating boxes equipped with closed circuit television for observing the rats during the sessions.

Drugs were injected i.p. immediately before the 1 hour daily sessions, which were always separated by at least one control (saline) session. All rats received each dose of both drugs in the following sequence: d-norpseudoephedrine-HCl (Knoll Fine Chemicals, New York) at 1.0, 10.0, 20.0, and 5.0 mg base/kg, and d-cathinone-HCl at 1.0, 5.0 and 0.5 mg base/kg. Drug effects are expressed as a percent of 7 saline control sessions for each rat. The response rates did not vary more than 10% over the control sessions for each rat, and the mean control response rate for the group was 83 ± 7 (M ± S.E.M.) responses/min. The parallel line bioassay (7) was used to calculate the dose of each drug which suppressed behavior 50% (ED_{50}) and the relative potency of the two drugs.

Results

Fig. 1 shows the dose-response relationship for d-norpseudoephedrine and cathinone for the one hour behavioral sessions. The parallel line bioassay

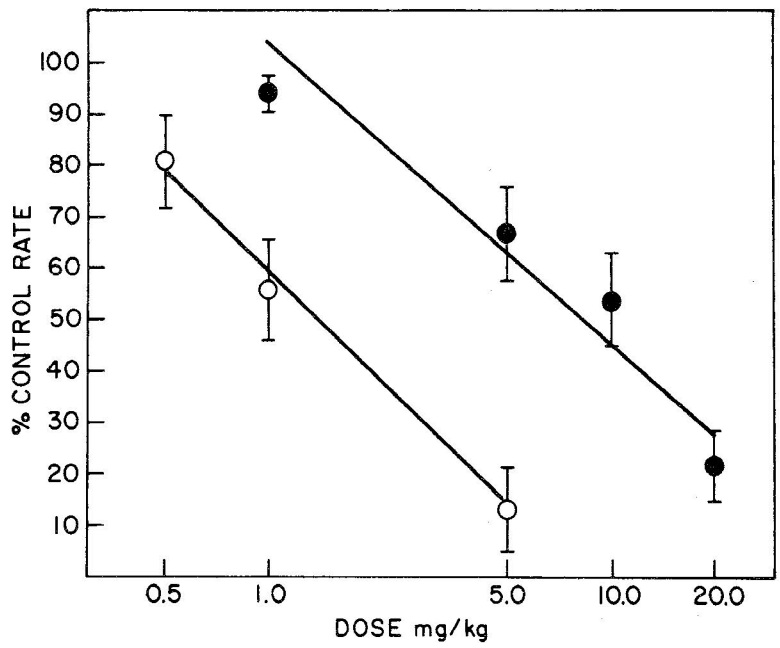

FIG. 1

Dose-response relationship for cathinone, open circles, and d-norpseudoephedrine, closed circles, on a 1 hour operant behavioral session. Response to the drug is expressed as a percent of the mean rate of 7 saline controls ± S.E.M. for the six rats at each dose. Each rat received all doses of both drugs.

indicated a significant regression for the lines ($F=40.2$, $df=1,30$; $p<0.01$) and that the lines were not significantly different from parallel ($F=0.09$, $df=1,30$; $p>0.1$). Cathinone is obviously more potent than d-norpseudoephedrine in suppressing FR 20 responding, with a calculated potency ratio equal to 6.8 (4.0-11.3, 95% confidence limits).

Examination of the cumulative response records for the drug sessions suggests the potency ratio calculated from this data may be confounded by differences in the time course of the two compounds. A comparison of the behavioral effects of 1 mg cathinone/kg with 10 mg d-norpseudoephedrine/kg shows that both totally suppressed responding but the duration of the effect was shorter for cathinone (fig. 2). Since responding usually returned to near normal rates in the latter half of the session, the measure of the response rate over the entire hour may underestimate the cathinone potency. If the behavioral effects are calculated for only the first 30 min of each session, the potency of d-norpseudoephedrine is little changed; ED_{50}=9.2 (6.3-13.2) mg/kg compared with 9.6 (6.3-14.5) mg/kg for the hour data. The ED_{50} for cathinone, however, decreased from 1.4 (1.0-2.0) mg/kg for the hour sessions to 0.9 (0.5-1.3) mg/kg for the first 30 min. The resultant potency ratio then becomes 10.7 (6.1-20.7) with this analysis of the first 30 min of each session.

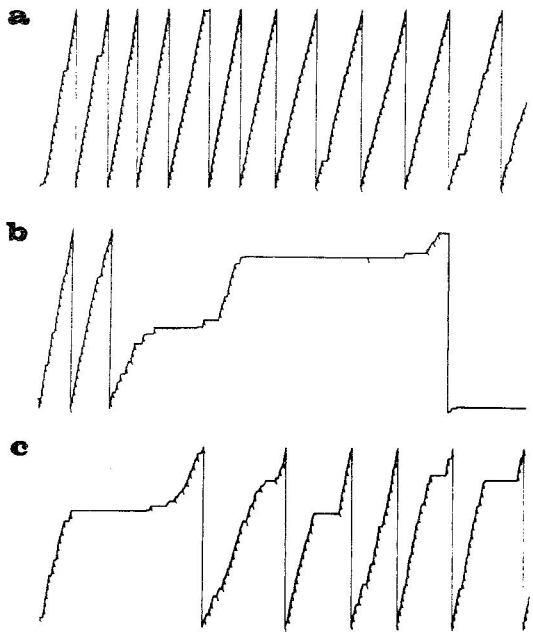

FIG. 2

Sample cumulative records for FR 20 responding for one rat (351) after i.p. saline (a), 10mg d-norpseudoephedrine (b), or 1mg cathinone/kg (c) injected immediately before a 1 hour behavioral session. The pen, denoting cumulative responses on the ordinate, reset after 440 responses. Backwards pips of the pen denote delivery of food pellets after each run of 20 responses.

Another apparent difference in the behavioral effects of these two drugs is the more rapid onset of cathinone's action. At approximately ED_{50} doses of each, the latency for total suppression of responding (a pause of >2 min) after 1 mg cathinone/kg, 4 ± 1 (M ± S.E.M.) min was significantly less than the 10 ±

1 min to onset after 10 mg d-norpseudoephedrine/kg (paired t-test, $p<0.05$).

Stereotyped movements, similar to amphetamine-induced behavior, were seen with both drugs. At the highest doses, intense, repetitive swaying and head bobbing movements were seen during and for some time after the sessions. Some stereotypy was also observed during and after the sessions following the injection of 10 mg d-norpseudoephedrine/kg. At 1 mg cathinone/kg, intense stereotypic movements were observed only early in the session, when responding was suppressed, but were totally absent by the end of the hour.

Discussion

In a recent report of the United Nations Narcotics Laboratory (8), it was suggested that the pharmacological study of the phenylalkylamines, cathinone and cathine (norpseudoephedrine) were considered essential to the future medical-legal control of khat abuse. Our report of a 7-10 fold greater potency of cathinone, relative to the previously proposed active component, d-norpseudoephedrine, is consistent with the idea that cathinone may be the more important component, since the cathinone content of fresh khat leaves is greater than that of d-norpseudoephedrine (8). This is significant because of the preference of experienced khat users for the very freshest of Catha leaves (2,9).

In man d-norpseudoephedrine is much less potent than is d-amphetamine as a CNS stimulant (10). In mice, d-norpseudoephedrine is 1/10th as potent as d-amphetamine in increasing locomotor activity (5). Therefore, based on the potency ratio we have determined in this study, we would predict that cathinone is comparable to amphetamine in its activity. This appears to hold true for the suppression of operant responding in rats, because the cathinone ED_{50} (0.9 mg/kg) is comparable to the ED_{50} of amphetamine (0.7 mg/kg) calculated in the same manner in an earlier study (6). Only through future reports of human consumption of khat of known phenylalkylamine content, will it be possible to determine if the activity of cathinone is sufficient to account for most of the stimulant action and/or abuse liability of this plant substance.

Further evidence for the greater importance of cathinone in the CNS activity of fresh khat can be derived from this behavioral study. The rapid onset and shorter duration of action of cathinone is consistant with the literature on human khat use. Halbach (2), in summarizing earlier reports of khat use, remarked on the surprisingly rapid onset of effects in volunteers ingesting the drug in the usual way, i.e. mastication. Similarly, the pattern of continuous intake of khat to maintain the desired effect (11) is consistent with the short duration of action of cathinone. There remains the possibility that the pattern of khat use is influenced by the degree of freshness of the material and/or tolerance to the active component(s) because only persons very experienced with the material have been included in the limited number of human studies.

Thus, the role of either or both of the phenylalkylamines in the CNS activity of khat cannot be fully defined without further pharmacological studies. A more complete pharmacological characterization of pure cathinone compared and contrasted with that of norpseudoephedrine should shed further light on the mechanism of action of the plant material as an abused stimulant source. Varying degree of freshness of the material, available to different geographic locations or to different socioeconomic segments of using populations, may be an important determinant of the consequences of acute and/or chronic use of khat. For example, consumption of material devoid of cathinone, for the pharmacological effects of cathine (norpseudoephedrine), may lead to behavioral and/or biochemical effects different from those observed after use of fresh khat. Therefore, it may be important to determine the relative amounts of the active phenylalkylamines absorbed or available for absorption during normal consumption of the Catha leaves.

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