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Anorexigenic Effects of Two Amines Obtained From *Catha edulis* Forsk. (Khat) in Rats

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ZELGER, J. L. AND E. A. CARLINI. *Anorexigenic effects of two amines obtained from* Catha edulis *Forsk. (Khat) in rats*. PHARMAC. BIOCHEM. BEHAV. 12(5)701–705, 1980.—The anorexigenic effects of cathine (phenylpropanolamine) and cathinone (α-aminopropiophenone), both amines obtained from *Catha edulis* Forsk. (Khat) were investigated by acute and chronic experiments in rats. Amphetamine was included for comparison purposes. Both khat amines reduced food intake when administered acutely and body weight when given chronically. Cathinone was more effective than cathine, and both were less active than amphetamine. Partial or total cross-tolerance was observed among the 3 drugs.

Catha edulis Forsk Khat Cathinone Cathine Amphetamine Food intake Body weight Tolerance Cross tolerance

FRESH leaves and tops of khat or tshaad (*Catha edulis* Forsk., Celastraceae) are widely used, since ancient times, in East Africa and the Arabic peninsula to reach a state of euphoria and stimulation [6, 15, 23].

Nor-pseudo-ephedrine or cathine (also known as phenylpropanolamine) identified in the plant in 1930 [26], has been considered until recently as the active principle responsible for the stimulant properties of khat [2,9]. In 1975, a new substance l-α-aminopropiophenone, called cathinone was isolated [24] and its structure established in 1978 [21]. As seen in Fig. 1 both substances are phenyl-propyl-amines and bear a close resemblance to the amphetamine structure.

Recent work in our laboratory [27,28] has shown that cathinone is able to increase motor activity in mice, and to induce stereotyped behavior in rats; the drug was about half as active as d-amphetamine and severalfold more potent than cathine. These results indicate that cathinone may actually be the main active principle in *Catha edulis*. Furthermore, the abolishment of cathinone effects by previous α-methyl-p-tyrosine treatment and the lack of effect of previous reserpine treatment revealed that the drug must act through the release of catecholamines (CA) from the labile pools [28]. This conclusion was strengthened by blockade of cathinone induced stereotyped behavior through the pretreatment with haloperidol [28].

On the other hand, appetite suppressant effects of khat chewing are reported since several centuries. As cited by Le Bras and Fretillere [13], Naguib Ad-Din, in 1237 prescribed in his "Livre de médicaments composés" the use of khat by warriors and messengers to relieve tiredness and hunger. Several other more recent reports also mention the anorexigenic effects of *Catha edulis* [6, 12, 15, 16, 17, 18, 19, 23].

The present report describes experiments performed in rats which test the eventual anorexigenic effects of cathinone and compare them with those of amphetamine and cathine. The latter drug which is widely used as an appetite suppressant has recently been extensively examined for its effects on food intake [7,8].

EXPERIMENT 1: ACUTE ADMINISTRATION

METHOD

Animals

Eighty two Wistar albino rats from our own colony, 3–4 months old and weighing 250–350 g were used. The animals housed in groups of 3, received food pellets and water ad lib. The temperature in the animal room, where the experiment was carried out, was 23±2°C, with a 12:12 hr light:dark cycle.

Drugs

The drugs used were: dl-amphetamine-sulphate (Sigma), referred to as amphetamine in this paper; d-nor-pseudo-ephedrine hydrochloride (Knoll), referred to as cathine; dl-α-amino-propiophenone (synthesized at the Institut of Pharmacy, University of Berne, Switzerland [18]), referred to as cathinone.

The drugs were dissolved in a 0.9% solution of NaCl, which served also as control solution. The doses of the drugs were calculated as the base of the corresponding salts. The injected volume was 0.1 ml/100 g of rats body weight.

Procedure

Control session. 20 hr before injection with saline, the animals were weighed and placed individually in wire cages measuring 30×20×15 cm. During this period they were food

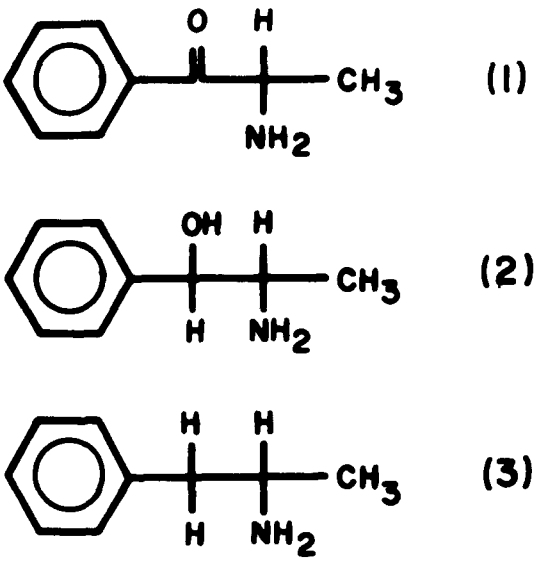

FIG. 1. Structural formulas of cathinone (1), cathine (2) and amphetamine (3).

deprived but had free access to water. Half an hour after injection a piece of carrot (70–100 g) was introduced into the cage and the amount ingested (in g±0.1 g) was recorded after 2 and 5 hr. At the end of this period the rats were returned to their homecages (3 per cage) with free access to food and water for the following 3 days. The use of a vegetable to test anorexia was based on a study made by Cross *et al.* [3] with potatoes.

In a preliminary test we observed that our rats prefer carrots to potatoes. The reason might be that carrot makes part of their diet during the first weeks of life, in addition to dry food pellets. This means that carrot is not really a novel stimulus to them. Even so, 2 rats showing a very low consumption of carrot which might indicate an abnormal neophobic behavior to the vegetable were eliminated from the study.

The reason for using carrot was essentially the higher consumption (in g) compared to dried food, which permits an easier distinction of feeding behavior between animals injected with different drugs and between the different doses of these drugs. Another reason was the easier measurement of the remaining food during and at the end of the experiment.

Experimental session. The animals were placed individually in the same wire cages and deprived of food during 20 hr. Groups of 8 rats with about the same average weight (274±42; 276±37; 278±39; 279±29; 279±37; 279±28; 279±46; 279±28, 281±38, 281±28 g) and about the same carrot consumption in the first session (35.5±5.2; 36.4±2.9; 37.2±10.3; 38.0±11.2; 38.0±11.6; 38.1±6.6; 38.5±5.5; 39.4±7.4; 39.6±9.6; 39.7±11.5 g) were IP injected each, with either saline, or 1, 2 or 4 mg/kg of cathinone, cathine or amphetamine. Thirty min later the animals received the pieces of carrot. Food consumption was recorded after 2 and 5 hr.

Statistical treatment. Differences in food consumption among the 10 groups were assessed by one way analysis of variance (F test) for each time period (0–2 hr; 2–5 hr; 0–5 hr). Statistical significance was reached when $p<0.05$.

Further comparisons between control and each experimental group were performed by using the two tailed Student's *t*-test, and $p<0.05$ was the critical level of significance.

TABLE 1

ACUTE EFFECTS OF CATHINONE, CATHINE AND AMPHETAMINE ON THE FOOD (CARROT) CONSUMPTION OF RATS. THE TIME INTERVAL BETWEEN THE INJECTIONS AND THE BEGINNING OF MEASUREMENTS WAS 30 min

Drug (mg/kg)		Food consumption (g ± SD) during 5 hr after drug injections 0–2 hr	2–5 hr	0–5 hr
Saline		23.0 ± 6.1	24.7 ± 6.6	47.8 ± 6.7
Cathinone	1	21.2 ± 5.0	22.1 ± 6.5	43.3 ± 4.8
	2	19.7 ± 5.8	24.7 ± 8.8	44.4 ± 8.3
	4	11.4 ± 5.8†	25.8 ± 4.8	37.2 ± 6.3†
Cathine	1	24.4 ± 4.8	22.3 ± 5.3	46.7 ± 4.8
	2	25.3 ± 5.9	21.5 ± 7.1	46.7 ± 8.5
	4	20.8 ± 5.9	16.7 ± 5.3	37.5 ± 8.2*
Amphetamine	1	18.5 ± 8.9	22.7 ± 6.0	41.2 ± 9.6
	2	12.4 ± 5.4†	22.1 ± 7.9	34.6 ± 9.3†
	4	7.6 ± 6.4‡	27.3 ± 5.6	34.9 ± 6.8†

Footnotes indicate statistically significant differences from saline-treated group (*$p\leq0.02$; †$p\leq0.01$, ‡$p\leq0.001$. Student's *t* test two-tailed).

RESULTS

The results are seen in Table 1. The F test revealed statistical differences at the time intervals 0–2 hr and 0–5 hr, F 0–2 hr $(9,70)=7.80$, $p<0.005$; F 2–5 hr $(9,70)=1.59$, $p<0.25$; n.s.; F 0–5 hr $(9,70)=3.66$, $p<0.025$. Saline treated rats ingested near the same amount of carrot in the first 2 hr (23.0 g±6.1) as in the following 3 hr (24.7±6.6), averaging a total consumption of 47.8 g±6.7 (first row of Table 1). The larger dose of cathinone and the 2 larger doses of amphetamine significantly reduced carrot consumption in the first 2 hr, but were not able to do so in the following 3 hr period. Nevertheless, the reduction achieved by these 2 drugs was significant for the whole 5 hr period. On the other hand, even the larger dose of cathine was not able to significantly reduce food consumption neither in the first 2 hr nor the last 3 hr measurement. However, statistical significance was achieved when considering the entire period of the experiment (0–5 hr).

EXPERIMENT 2: CHRONIC ADMINISTRATION (DEVELOPMENT OF TOLERANCE)

METHOD

Animals

Forty male albino rats, aged 5–6 months and weighing between 300–400 g, were divided into 4 groups of 10 animals with about the same average weight at the beginning of the experiment (339.5±34; 339.5±41; 340.0±22; 340.5±37 g). The animals were housed and tested in wire cages with 2 or 3 rats/cage.

Drugs

The same as in Experiment 1.

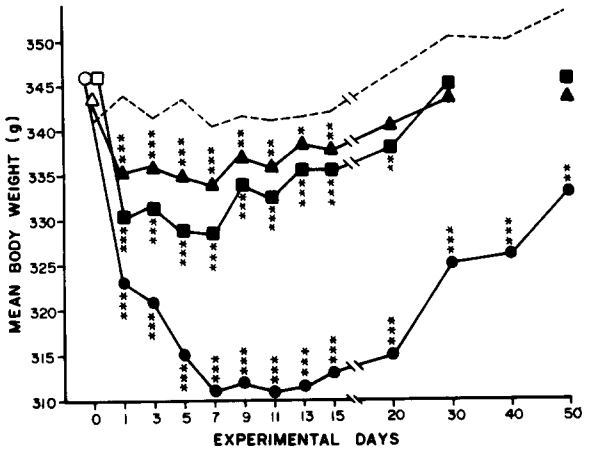

FIG. 2. Effects of cathinone, cathine and amphetamine on the body weight of rats adapted to 4 hr food consumption daily. The open symbols represent the average body weight on the last day after a 17 day period of adaptation. The heavy symbols indicate the body weight during drug administration: 4 mg/kg cathine (triangles), 4 mg/kg cathinone (squares), 4 mg/kg amphetamine (circles) and saline (dashed line). Asterisks indicate statistically significant differences when compared to the pre-drug value (*$p<0.05$; **$p<0.01$; ***$p<0.001$. Paired Student's t-test).

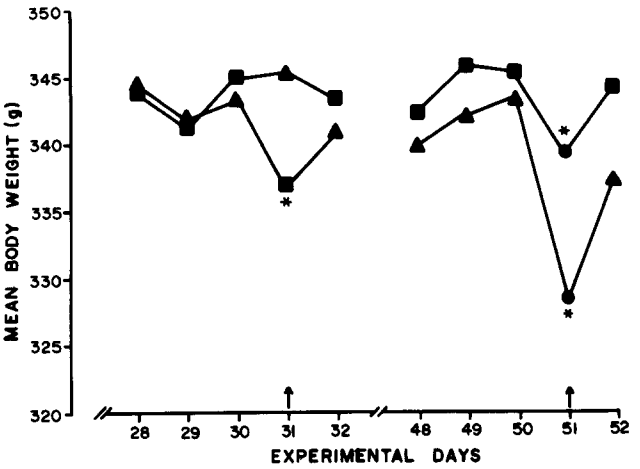

FIG. 3. Effects of a single injection (↑) of 4 mg/kg of cathine (Day 31) or amphetamine (Day 51) on the body weight of cathinone-tolerant animals, and of 4 mg of cathinone or amphetamine on the body weight of cathine-tolerant animals. The symbols used are the same as in Fig. 2. *Indicates a significant difference when compared to the previous day ($p \leq 0.001$, Paired Student's t-test).

Procedure

During a 17 day period of adaptation the rats had free access to food pellets for only 4 hr/day (from 12:00–16:00 hr) with water available continuously. A saline IP injection was given daily 15 min before food presentation, and after the 4 hr period of feeding the body weight was recorded. After this predrug period all the groups had returned at least to their initial weight. One group then continued to be injected with saline while the other 3 groups were daily injected IP with 4 mg/kg of amphetamine, cathinone or cathine. The experiment was run for at least 30 days and the rats were weighed after each food session.

RESULTS

The curves in Fig. 2 represent the results of 50 days of experiment. All 3 drugs produced a significant reduction in body weight, being amphetamine the most active, and cathine the least. The effects disappeared within 20–30 days for cathine and cathinone and persisted for at least 50 days for amphetamine. It is also seen that development of tolerance began around Day 7 for both khat compounds and by Day 13 for amphetamine.

EXPERIMENT 3: CROSS TOLERANCE STUDIES

METHOD

Animals

The animals injected with cathinone or cathine in Experiment 2 were used.

Drugs

The same as in Experiment 1.

Procedure

After the cathinone- and cathine-treated animals had returned to their predrug baseline weight, (Day 30 in Experiment 2), cross-tolerance was tested between the 2 drugs by a single injection of cathine (4 mg/kg) to the cathinone-tolerant animals and cathinone (4 mg/kg) to the cathine-tolerant rats. The following day the rats were put back to their previous drug administration schedules for 20 more days. Subsequently they were tested for tolerance to amphetamine (4 mg/kg) and then returned to the initial schedule for 1 more day. Following that, the rats were injected during 15 days with saline.

RESULTS

The rats tolerant to 4 mg/kg of cathinone revealed a complete cross-tolerance to 4 mg/kg of cathine, but the reverse was not true as animals tolerant to cathine still reacted to cathinone (Fig. 3, Day 31). However, the reaction revealed a partial tolerance since cathinone, when given for the first time, induced 16.5 g of weight loss (Fig. 2, Day 1) whereas in cathine-tolerant-rats the loss was only 6.5 g (Fig. 3). When amphetamine was tested in the two tolerant groups (Fig. 3, Day 51) the drug significantly reduced body weight in cathine- and cathinone-tolerant animals. Partial tolerance, was noted, mainly with cathinone-tolerant rats in which amphetamine induced only 6 g of weight loss against the 23 g loss when it was first administered (Fig. 2, Day 1).

After Day 52, the animals from all 4 groups were treated with saline for 15 more days. Cathinone-, cathine- and amphetamine-treated rats recovered weight rapidly and at the end they were equal to the control group, $F(3,36)=0.179$, $p>0.50$.

DISCUSSION

The anecdotal descriptions that khat chewing produces, in addition to central stimulant effects, anorexia in human beings [6, 12, 13, 15, 16, 17, 18, 19, 23] are supported by our data. They show that cathinone possesses anorexigenic properties in rats, which were observed in acute as well as in

chronic treatment studies. Cathine also showed activity in both test situations, but its effect was less pronounced, specially if we consider that the more active d-isomer of cathine [9] was tested, while cathinone was used in its racemic form. The results of Table 1 show that, even if there is no significant detectable difference by analysis of variance neither during the first 2 nor the 3 following hr, the 4 mg/kg dose of cathine produced a significant overall food intake reduction (0–5 hr after food presentation), which is mainly due to diminished eating during the second part of the experiment (2–5 hr). This contrasts with the data obtained for cathinone and amphetamine, which, at higher doses, are active during the first 2 hr period. These results go parallel to our earlier findings for locomotion and stereotypies [27,28], in which cathinone similarly to amphetamine induced a high initial effect followed by a rapid decline, while cathine produced a somewhat retarded and slow increase in locomotion and stereotyped behavior, persisting for a longer time. Beyond this, a higher dose of cathine was needed to produce behavioral effects similar to those of cathinone.

Tolerance to the effects of the two amines of khat began after a 7 day period of continuous weight loss (Fig. 2); recovery to predrug baseline weight was obtained after 20 days for cathine and after 30 days for cathinone. But even after a 50 day period cathine- and cathinone-treated rats did not reach the weight of the saline-treated animals. The group injected with 4 mg/kg of amphetamine did not return to baseline values during the 50 days of experiment. However, once the drug treatment stopped, the rats gained body weight rapidly, and after 15 days there was no longer a detectable difference between the 4 groups.

Experiment 3 revealed that partial or total cross-tolerance occurred among the 3 amines. These results suggest that the anorexigenic effects of cathinone and cathine may involve a mechanism of action similar to that of amphetamine. There exists evidence that brain catecholamines (CA) are implicated in the anorexigenic activity of amphetamine and other structurally related compounds [1, 4, 10, 11, 14, 20]. Actually, our previous results have shown that cathinone and cathine need, like amphetamine, recently synthesized CA to be active [28]. Furthermore, the development of total or partial cross-tolerance could indicate the relative strength of the amines in relation to each other and to amphetamine.

In the case of cathine, the requirement of higher doses and its retarded action could be explained by the difficulty of penetrating the CNS [5,25], or by a mechanism different from that producing amphetamine-anorexia [7,8].

Our previous findings that cathinone is more potent than cathine in the tests for locomotor activity and stereotyped behavior are now extended to the anorexigenic effect, even though in the latter case the difference between cathinone and cathine is less pronounced. This higher potency of cathinone would explain the preference of khat consumers for fresh leaves and tops which contain a higher concentration of cathinone than of cathine [22]; older and dry plant material, which is reported to be less active [6, 13, 18] contains mostly cathine, formed probably by biotransformation from cathinone [22].

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