European Journal of Pharmacology, 68 (1980) 213—215

Short communication

A CONSTITUENT OF KHAT LEAVES WITH AMPHETAMINE-LIKE RELEASING PROPERTIES

PETER KALIX

Department of Pharmacology, University of Geneva, 20 Rue de l'Ecole de Médicine, CH 1211 Genève 4, Switzerland

Received 13 August 1980, revised MS received 3 October 1980, accepted 7 October 1980

P. KALIX, *A constituent of khat leaves with amphetamine-like releasing properties*, European J. Pharmacol. 68 (1980) 213—215.

Khat leaves, which are widely abused as a stimulant, contain the alkaloid (—)-cathinone. The effect of this compound on the efflux of radioactivity from rabbit striatal tissue prelabelled with [^{3}H]dopamine was examined. (—)-Cathinone enhanced the release of label, and was found to have a potency similar to that of (+)-amphetamine. The observation demonstrates that the khat alkaloid also has amphetamine-like effects at the cellular level.

Amphetamine Cathinone Release

1. Introduction

In certain countries of East Africa and the Arab Peninsula, fresh leaves of the khat shrub (*Catha edulis*, Celastraceae) are widely used as a stimulant. The World Health Organization and the UN Narcotics Commission have become preoccupied with the situation, since the habit of chewing khat creates socio-economic problems to both the individual and the community (WHO Technical Reports, 1964). The UN Narcotics Laboratory has recently succeeded in isolating and identifying a new khat alkaloid, for which the name (—)-cathinone has been proposed (UN Document, 1975). Chemically, (—)-cathinone is S-(—)-α-aminopropiophenone (Schorno and Steinegger, 1979); it thus bears close resemblance to amphetamine. An examination of the pharmacological properties of this compound appeared pertinent.

The effects induced by the chewing of khat are highly reminiscent of those of amphetamine (Halbach, 1972). Indeed, some recent findings indicate that the khat alkaloid and (+)-amphetamine are pharmacologically quite similar. For example, both substances stimulate locomotor activity (Kalix, 1980a) and cause a rise in body temperature (Kalix, 1980b). Amphetamine is thought to act for the most part as an indirect sympathomimetic, i.e. through release of catecholamines from presynaptic storage sites. In this context, amphetamine has been shown repeatedly to induce the release of dopamine from striatal preparations that had been prelabelled with either this neurotransmitter or its precursors (see for example Nowycky et al., 1975). The experiments reported in the following show that (—)-cathinone can mimic (+)-amphetamine in this respect and they demonstrate that the effects of (+)-amphetamine and (—)-cathinone are similar at the cellular level.

2. Materials and methods

Samples of rabbit striatum, dissected at the limit between the corpus and the tail of the

caudate nucleus immediately after killing of the animals, were cut with a razor blade into cubes measuring not more than 1 mm in each dimension. These cubes were then incubated for 20 min at 37°C in 1 ml of a solution containing (mmol/l) NaCl 136; KCl 5.6; $NaHCO_3$ 20.0; NaH_2PO_4 1.2; $CaCl_2$ 2.2; $MgCl_2$ 1.2; glucose 5.5; ascorbic acid 0.28 to which 12 μCi [^{3}H]dopamine (1.2 nmol dopamine) had been added. During the incubation (as well as during the subsequent superfusion) the medium was continuously oxygenated with a mixture of 95% O_2—5% CO_2, its pH was 7.3. At the end of the labelling period two of the tissue samples were transferred to a perspex chamber of approximately 0.3 ml volume and superfused at a rate of 0.5 ml/min with the above solution at 37°C. The spontaneous efflux of label stabilized during an initial washing period of one hour to a steady background which was not altered by the flow stop of about 3 sec necessary for switching to a modified superfusion medium. During the subsequent experimental period, the superfusate was collected in successive 3 min fractions, its radioactivity was then determined after addition of 12 ml hydrophilic scintillation fluid. All individual experiments were run in duplicate.

3. Results

The presence of low concentrations of (—)-cathinone in the solution superfusing the striatal tissue was found to result in a rapid and reversible increase of the release of radioactivity (fig. 1). This effect was dose-dependent and already perceptible at concentrations below 1 μM. By contrast, (+)-norpseudoephedrine, an alkaloid that is also present in khat leaves and that is structurally an intermediate between (—)-cathinone and (+)-amphetamine, did not cause an increase of the release of radioactivity from the tissue.

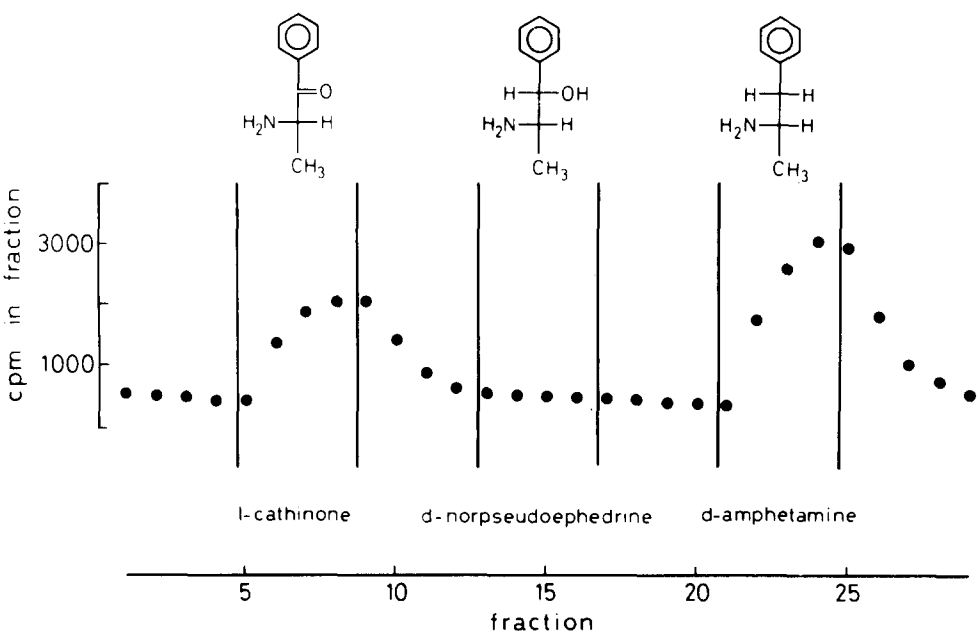

Fig. 1. The effect of (—)-cathinone, (+)-norpseudoephedrine and (+)-amphetamine, at a concentration of 4 μM, on the efflux of radioactivity from rabbit striatal tissue prelabelled with [^{3}H]dopamine.

4. Discussion

The observations described above demonstrate that (—)-cathinone is an alkaloid with amphetamine-like releasing properties and that it has, in this respect, a potency comparable to that of (+)-amphetamine. (—)-Cathinone has recently been reported to mimic (+)-amphetamine in inducing stereotypical oral activity (Kalix, 1980a,b) and in stimulating locomotor activity (Kalix, 1980a). Since the nigrostriatal dopamine pathway is supposed to be involved in the induction of these effects by amphetamine (Creese and Iversen, 1975), it would appear that (—)-cathinone and (+)-amphetamine produce their behavioural effects by acting at the same site. Although (+)-norpseudoephedrine, another alkaloid present in *Catha edulis*, was formerly thought to be the active principle of the plant (Winterfeld and Bernsmann, 1960; Alles et al., 1961), its ineffectiveness in enhancing the efflux from prelabelled striatal tissue lends support to the subsequent assumption (Friebel and Brilla, 1963) that the stimulant properties of khat are mainly due to another constituent, probably (—)-cathinone (Schorno and Steinegger, 1979). The results of the experiments described here, taken together with previous observations (Kalix, 1980a,b), suggest that the widespread habit of chewing khat is pharmacologically equivalent to amphetamine abuse.

Acknowledgements

I am grateful to Dr. O. Braenden (United Nations Narcotics Laboratory) for a sample of (—)-cathinone, to Dr. J. Müller (Cooper SA, Fribourg, Switzerland) for (+)-norpseudoephedrine and to Mrs. Judith Noebels for her effective help with the editing.

References

Alles, G., M. Fairchild and M. Jensen, 1961, Chemical pharmacology of *Catha edulis*, J. Med. Pharm. Chem. 3, 323.

Creese, I. and C. Iversen, 1975, The pharmacological and anatomical substrates of the amphetamine response in the rat, Brain Res. 83, 419.

Friebel, H. and R. Brilla, 1963, Über den zentralerregenden Wirkstoff der frischen Blätter und Zweigspitzen von *Catha edulis* Forskal, Naturwissenschaften 50, 354.

Halbach, H., 1972, Medical aspects of the chewing of khat leaves, Bull. Wld. Hlth. Org. 47, 21.

Kalix, P., 1980a, Hypermotility of the amphetamine type induced by a constituent of khat leaves, Br. J. Pharmacol. 68, 11.

Kalix, P., 1980b, Hyperthermic response to (—)-cathinone, an alkaloid of *Catha edulis* (khat), J. Pharm. (in press).

Nowycky, M., G. Scaragli, J. Cooper and R. Roth, 1975, Effect of collagenase on the release of dopamine and acetylcholine from slices of rat corpus striatum, J. Neurochem. 24, 1279.

Schorno, X. and E. Steinegger, 1979, CNS-active phenylpropylamines of *Catha edulis* of Kenyan origin, Experientia 35, 572.

United Nations Document, 1975, Etudes sur la composition chimique du khat. Recherches sur la fraction phénylalkylamine, UN Document MNAR/11/1975.

World Health Organization Expert Committee on Addiction Producing Drugs, 1964, Thirteenth report, Wld. Hlth. Org. Techn. Rep. Ser. 273, 10.