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Khat: an amphetamine-like plant material*

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The chewing of leaves of the khat shrub is common in certain countries of East Africa and the Arabian peninsula, and many khat users are subject to psychic dependence on the drug. The syndrome observed after khat consumption is characterized by a certain degree of CNS stimulation and by sympathomimetic effects; it is reminiscent of that induced by amphetamine.

Recently, the alkaloid (–)-cathinone has been isolated from khat leaves and this substance produces effects in animals that are analogous to those of (+)-amphetamine and that correlate well with the effects observed in humans after khat consumption. Furthermore, it has been shown that (–)-cathinone acts by the same mechanism as (+)-amphetamine, i.e., by inducing release at physiological catecholamine storage sites. Taken together, these studies indicate that khat must be considered an amphetamine-like material.

The detrimental effect on public health of the non-medical use of drugs is an important aspect to consider in the context of the activities of the World Health Organization whose present goal is health for all by the year 2000. Drug abuse problems are not only due to synthetic substances, but may also be caused by plant material. A pertinent example is the use of leaves of the khat shrub as a stimulant, a habit that is widespread in certain countries of the Arabian peninsula and East Africa. Several years ago, the United Nations Narcotics Laboratory succeeded in isolating a new alkaloid, (–)-cathinone, from khat leaves and this compound was found to be a "natural amphetamine" and largely responsible for the effects observed after chewing khat. The purpose of this update is to describe the khat habit and, in particular, the pharmacological studies that have recently been carried out with (–)-cathinone, a substance that is now known to be the main constituent of khat.

CONSEQUENCES OF CHEWING KHAT

The first written account of the chewing of khat appeared more than seven centuries ago in an Arabic medical book, and the use of khat as a stimulant is thought to antedate that of coffee. Today, several million people are habitual khat chewers. The use of the material was confined to the regions where the plant was grown because only the fresh leaves gave the desired stimulating effect, but in recent years the habit has expanded considerably because of air transportation of khat to distant places. Cultivation and consumption of khat have profound socioeconomic consequences for the countries concerned and the use of khat has considerable impact on the life of the individual. Khat chewers are mostly male and the harm to their families is due to negligence, dissipation of family income, and inappropriate behaviour. Many of them secure their daily portion of khat at the expense of vital needs, which indicates psychic dependence.

* A French translation of this article will appear in a later issue of the *Bulletin*.

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The effects of khat

The main effects of chewing khat are a moderate degree of euphoria and excitation often accompanied by loquacity (*1*). High doses may induce hyperactivity and, sometimes, manic behaviour. Although there have been several reports of cases of psychosis due to khat chewing, this is rather exceptional, probably because of the physical limits to the dose that can be absorbed. Khat is an effective anorectic, which largely explains the malnutrition often seen in habitual khat users, and it also causes hyperthermia and an increase in respiration. The peripheral effects of khat chewing are of the sympathomimetic type and generally include hypertension and mydriasis. Another frequent symptom is constipation, but this is probably related to the tannin content of the leaves. The effects of khat are, of course, difficult to quantify since the leaves are a non-standardized material, the potency of which depends on freshness and origin, and there are certainly differences between chewers in the efficiency of the mastication process.

THE ACTIVE PRINCIPLE

Although the first efforts to identify the active principle of khat date back to the last century, it was Wolfes (*2*) who, probably working with dried material, isolated in 1930 (+)-norpseudoephedrine from the leaves and this substance was then believed to be the main active principle of khat. It was later pointed out, however, that (+)-norpseudoephedrine is a stimulant of rather low potency and that the amount of the substance present in a portion of khat would be insufficient to account for the symptoms observed after its consumption. In the early 1960s, therefore, Friebel & Brilla (*3*) investigated extracts of lyophilized fresh khat and were successful in isolating an alkaloid whose chemical structure they were unable to identify, but which was found to be considerably more potent than (+)-norpseudoephedrine in stimulating the motor activity of mice. Since this substance, possibly because of its great lability, could not be detected in the dried leaves, it was suggested that a conversion to (+)-norpseudoephedrine occurred during the drying process.

The international organizations were confronted with the problems associated with khat as early as 1935, when the League of Nations Advisory Committee on the Traffic of Dangerous Drugs discussed two technical reports on the subject. Through the United Nations Commission on Narcotic Drugs, international attention was once again directed to the nature and extent of khat use and in 1971 the Commission recommended that the United Nations Narcotics Laboratory should reinvestigate the chemical composition of khat. These studies led to the isolation of S-(−)-α-aminopropiophenone from khat leaves, an alkaloid that is chemically similar to amphetamine (Fig. 1) and for which the name (−)-cathinone was suggested. Subsequently it was found (*4*) that in certain khat samples, the phenylalkylamine fraction consisted of up to 70% of (−)-cathinone and that the (−)-cathinone content correlated with the market price of khat.

Studies on (−)-cathinone

Once (−)-cathinone was recognized as the major active principle of the leaves, the substance was synthesized and made available to pharmacologists through the World Health Organization, which also appointed an advisory group that carried out the initial survey of the pharmacological properties of the new alkaloid (*5–9*). These studies revealed that the pharmacological profile of (−)-cathinone closely resembles that of (+)-amphetamine. It was observed, for example, that (−)-cathinone had a positive inotropic and chronotropic effect on isolated guinea-pig heart, and that it caused a substantial

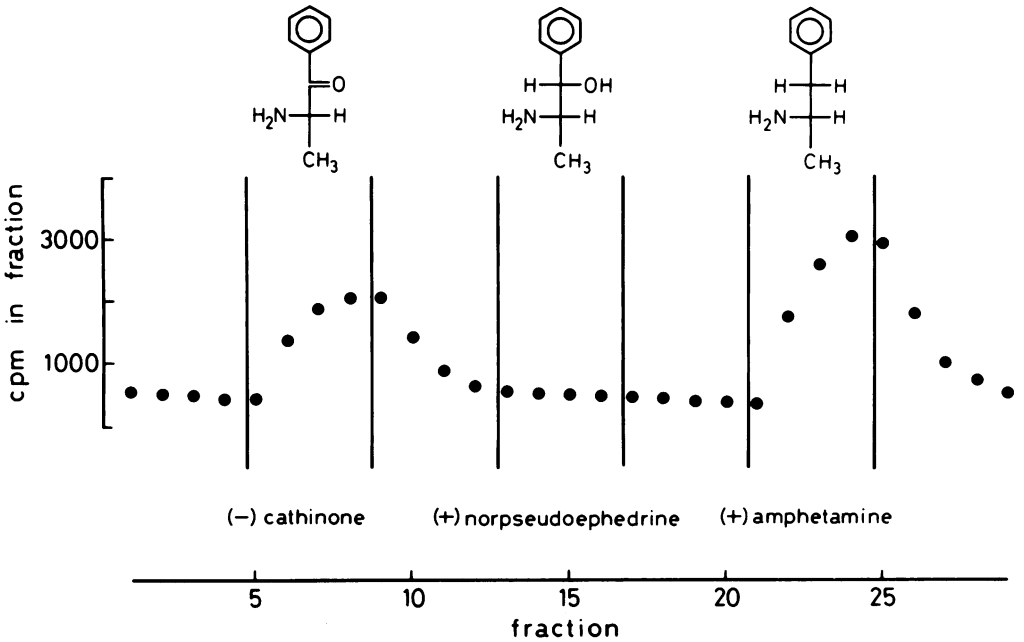

Fig. 1. The effect of (−)-cathinone, (+)-norpseudoephedrine and (+)-amphetamine, at a concentration of 4 μmol/l, on the release of radioactivity from isolated rabbit caudate nucleus prelabelled with ^{3}H-dopamine. Each fraction corresponds to 3 min of efflux. For details, see reference *13*.

increase in blood pressure when injected to anaesthetized cats or rats. In the isolated rabbit ear artery, constrictions induced by low frequency stimulation were potentiated by (−)-cathinone, whose potency in this respect was similar to that of (+)-amphetamine. Taken together, the studies of the peripheral effects of (−)-cathinone suggest that the alkaloid acts by facilitating noradrenergic transmission and is responsible for the sympathomimetic syndrome observed after khat consumption.

Since khat is used as a stimulant, the behavioural effects observed within the context of this survey are of particular importance. It was found that the effect of (−)-cathinone on the locomotor activity of mice corresponded to that of (+)-amphetamine. It was also found that (−)-cathinone was an anorectic almost as potent as (+)-amphetamine, and that cross tolerance between the effects of the two compounds occurred (*10*). Close similarities between (−)-cathinone and (+)-amphetamine were also observed with regard to their effect in animals whose behaviour had been conditioned by scheduled food delivery. Furthermore, it was observed that in rats trained to distinguish between placebo and (+)-amphetamine, (−)-cathinone could be used as a substitute for (+)-amphetamine. It was also demonstrated that in monkeys trained to press a lever for cocaine injections, (−)-cathinone functioned as a reinforcer to elicit very high rates of responding and was, in this respect, even more potent than (+)-amphetamine. The self-administration pattern observed in these experiments was that of the "spree-type", i.e., the animals took the drug frequently day and night, stopping only upon becoming exhausted, and beginning again after recovery. This pattern corresponds to that seen in amphetamine-dependent humans. Taken together, these findings indicate that (−)-cathinone is a potent amphetamine-like compound and the constituent of khat mainly responsible for the CNS effects (Table 1). Since (−)-cathinone enhances behaviour of test animals that results in the availability of this substance to them, it can be assumed that the alkaloid is the dependence-producing constituent of khat.

Table 1. Common features in the effects of khat in man and of (−)-cathinone in animals

Effects of khat chewing in humans	Effects of cathinone in animals
Anorexia	Anorexia (rat, monkey)
Insomnia, lack of fatigue	Restlessness (monkey)
Hyperactivity	Hypermotility (mouse, rat)
Excitation	Stereotyped oral activity (mouse, rat, rabbit)
Euphoria	
Logorrhoea	
Hyperthermia	Hyperthermia (rabbit)
Increased respiration	Increased oxygen consumption (rat)
Mydriasis	Mydriasis (monkey)
Arrhythmias	Positive inotropic and chronotropic effect (guinea pig atrium)
Hypertension	Hypertension (cat)
Constipation (probably due to tannins)	
Compulsive khat consumption	Cathinone self-administration (monkey)

The initial studies of the WHO Advisory Group (*9*) were extended in several directions. For example, Zelger et al. (*11*) showed that rats injected with (−)-cathinone displayed stereotypical behaviour corresponding to that seen after (+)-amphetamine administration. Nencini (*12*) investigated the analgesic properties of (−)-cathinone as well as its effects on some endocrine and metabolic parameters; in both cases a close parallelism between (−)-cathinone and (+)-amphetamine was observed. Other studies focused on the mechanism of action of (−)-cathinone. Since induction of catecholamine release is believed to be the main cellular effect of (+)-amphetamine, the question arose as to whether this was also the case for (−)-cathinone. When slices of rabbit caudate nucleus that had been prelabelled with ^{3}H-dopamine were superfused with a solution of (−)-cathinone, a rapid and reversible increase of the efflux of label was indeed seen to occur (*13*), and (−)-cathinone was found to be almost as potent as (+)-amphetamine in this respect (Fig. 1). On the other hand, an eight times higher concentration of (+)-norpseudoephedrine was required to reproduce the effect of a given dose of (−)-cathinone, and this ratio of potency for the two khat alkaloids is similar to that observed in some of the pharmacological studies of the previously discussed survey. In further experiments, it was shown that the catecholamine releasing effect of (−)-cathinone could be modified by the same pharmacological procedures as that of (+)-amphetamine, and that it occurred also in other brain areas known to mediate amphetamine effects. Finally, it was found that (−)-cathinone also induced release of catecholamine from rabbit heart tissue prelabelled with ^{3}H-noradrenaline (*14*). These observations demonstrate that the new khat alkaloid (−)-cathinone acts by inducing release from physiological catecholamine storage sites.

CONTROLLING THE PROBLEM

An evaluation of the pharmacology of khat indicates that the effects of the drug can be explained by the presence of (−)-cathinone in the leaves, and that this alkaloid is a substance with pharmacological properties analogous to those of (+)-amphetamine and of

similar potency. Thus, in terms of pharmacology, the chewing of a portion of khat is tantamount to ingesting amphetamine—a fact discovered mainly through the impetus given by the World Health Organization for the pharmacological investigation of the new compound. The finding that (−)-cathinone is a potent amphetamine-like substance shows that there is a certain degree of danger associated with khat use. Although immediate and severe medical problems arising from khat consumption are infrequent (because the (−)-cathinone is diluted in the other material of the leaves), the use of khat presents a health problem, and this, taken together with the serious socioeconomic consequences of the habit, makes its limitation desirable. Effective reduction of the use of khat would relieve several million people of a costly, counterproductive and often addictive habit, and it would even make available scarce arable land and irrigation water that are, at present, used for the cultivation of khat.

Several countries concerned by the khat problem are now taking steps to restrict the use of the material. In order to catalyse these efforts, WHO has sponsored field studies on the medical (*1*) and epidemiological[a] aspects of khat chewing, and a WHO intercountry meeting on the health, social and economic aspects of khat was held recently.[b] On the other hand, there is the responsibility of WHO to advise the Secretary-General of the United Nations on the need for control of dependence-inducing substances, and in this perspective the abuse potential of (−)-cathinone is to be evaluated early in 1985 by a WHO Expert Committee.

REFERENCES

1. HALBACH, H. Medical aspects of the chewing of khat leaves. *Bulletin of the World Health Organization*, **47**: 21–29 (1972).
2. WOLFES, O. Über das Vorkommen von *d*-nor-iso-ephedrin in *Catha edulis*. *Archiv der Pharmazie*, **268**: 81–83 (1930).
3. FRIEBEL, H. & BRILLA, R. Über den Wirkstoff der frischen Blätter und Zweigspitzen von *Catha edulis*. *Naturwissenschaften*, **50**: 354–355 (1963).
4. SCHORNO, X. ET AL. Qualitative und quantitative Untersuchungen über das Vorkommen ZNS-aktiver Phenylpropylamine in Handelsdrogen und über deren Verteilung in verschiedenen Organen von *Catha edulis*. *Pharmaceutica Acta Helvetica*, **57**: 168–176 (1982).
5. KNOLL, J. Studies on the effects of (−)-cathinone. In: *Problems of drug dependence 1979* (NIDA Research Monograph **27**). Washington, US Government Printing Office, 1980, pp. 322–323.
6. SCHUSTER, C. & JOHANSON, C. Behavioural studies of cathinone in monkeys and rats. In: *Problems of drug dependence 1979* (NIDA Research Monograph **27**). Washington, US Government Printing Office, 1980, pp. 324–325.
7. YANAGITA, T. Studies on cathinones: cardiovascular and behavioural effects in rats and self-administration experiments in monkeys. In: *Problems of drug dependence 1979* (NIDA Research Monograph **27**). Washington, US Government Printing Office, 1980, pp. 326–327.
8. ROSECRANS, J. ET AL. Discriminative stimulus and neurochemical mechanism of cathinone: a preliminary study. In: *Problems of drug dependence 1979* (NIDA Research Monograph **27**). Washington, US Government Printing Office, 1980, pp. 328–329.
9. WHO ADVISORY GROUP. Review on the pharmacology of khat. *Bulletin on narcotics*, **32**: 83–93 (1980).
10. FOLTIN, R. & SCHUSTER, C. Behavioural tolerance and cross-tolerance to *dl*-cathinone and *d*-amphetamine in rats. *Journal of pharmacology and experimental therapeutics*, **222**: 126–131 (1982).

[a] BAASHER, T. & SADOUN, R. *The epidemiology of khat chewing in the Republic of Djibouti*. Unpublished WHO document EM/MENT/102 (1983).

[b] Meeting in Mogadishu, Somalia, October 1983 (unpublished WHO document EM/MENT/103 (1983)).

11. ZELGER, J. ET AL. Behavioural effects of cathinone, an amine obtained from *Catha edulis*: comparisons with amphetamine, norpseudoephedrine, apomorphine and nomifensine. *Bulletin on narcotics*, **32**: 67–81 (1980).
12. NENCINI, P. Cathinone, active principle of the khat leaf: its effect on *in vivo* and *in vitro* lipolysis. *Pharmacological research communications*, **12**: 855–861 (1980).
13. KALIX, P. A constituent of khat leaves with amphetamine-like releasing properties. *European journal of pharmacology*, **68**: 213–215 (1980).
14. KALIX, P. Effect of the alkaloid (−)-cathinone on the release of radioactivity from rabbit atria prelabelled with ^{3}H-norepinephrine. *Life sciences*, **32**: 801–807 (1983).