Short Communication

KHAT, AN AMPHETAMINE-LIKE STIMULANT

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Long before the advent of chemically defined psychoactive substances, humans used drugs of natural origin to induce feelings of pleasure and euphoria, and in certain regions of the world this is still the case. A pertinent example is the use of leaves of the khat bush as a stimulant, a habit that is prevalent in some countries of East Africa and of the Arab Peninsula. The effects of this material are similar to those of amphetamine (Halbach 1972; Eddy et al. 1965; Hodgkinson 1962) although their intensity is usually low, which is explained by the dose limit set by the volume of the material. Another limitation for the use of this drug is that the leaves lose their effectiveness when they wilt, and this has confined the habit of chewing khat more or less to areas where the plant grows. However, motorization and road building have led to more efficient distribution of this perishable drug, which has brought about a notable proliferation of khat use; presently the consumption is estimated at some five million portions per day.

In addition, due to the possibility of rapid air transport, the drug has now made its appearance in London (Gough & Cookson 1984), Rome (Nencini et al. 1989), New York (Browne 1990), Amsterdam (Max 1991), and in Canada (LeBelle, Lauriault & Lavoie 1993). At the same time, severe khat intoxications have been reported from the United States (Giannini & Castellani 1982) and Great Britain (Pantelis, Hindler & Taylor 1989; Critchlow & Seifert 1987; McLaren 1987; Gough & Cookson 1984). There have been administrative steps taken to proscribe khat. In the United States, for example, it has recently been included in Schedule I of the Controlled Substances Act. On the other hand, the public has become aware of this exotic drug through media reports pertaining to the United Nations mission in Somalia, a country which is among those where khat use is endemic. Consequently, this article briefly describes the khat habit and summarizes some of the pharmacological studies pertaining to the psychoactive constituents of this drug.

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USE

The khat plant is known by a variety of names, such as *qat* in Yemen, *tschat* in Ethopia, and *miraa* in Kenya; its botanical name is *Catha edulis*. The drug consists of the sprouts and leafy tops of the branches, which are usually straight and have alternate or opposite leaves. These are brownish green with a glossy upper surface, leathery, and have a serrated edge. In general, the material is harvested in the early hours of the day and then transported speedily to the markets while being kept moist; it is generally sold by late morning. The buyer chooses among the various types of khat available, and he may meet some time after noon with other chewers for a common khat session.

Traditionally, khat has been used as a socializing drug, and this is still very much the case in Yemen (Kennedy 1987; Weir 1985; Schopen 1978). Here, the chewers gather in the living room of a host's house, and they begin to masticate the leaves one by one while swallowing the juice and rejecting the residues; usually, a participant takes 100 to 200 grams. The young leaves from the tips of the branches are favored because they are more potent and also because of their tenderness.

During the chewing process there are lively discussions often pertaining to matters of general interest, and in this way the khat session catalyzes social interaction and integration. Especially in Yemen, khat chewing is a predominantly male habit; the sessions of women are infrequent and much less formal. In other countries, however, khat is also consumed largely by single individuals and at parties that lack the stringent and well-defined social context mentioned above. Thus, khat is mainly a recreational drug, even though it may also be used by farmers and laborers for reducing physical fatigue, and by drivers and students for improving attention. Of course, it is often difficult to decide on the motives that determine the khat use of a given individual; that is, to distinguish if the drug is taken for enhancing sociability and withstanding fatigue, or if the intention simply is to enjoy its pleasurable stimulant and euphoriant effects.

EFFECTS

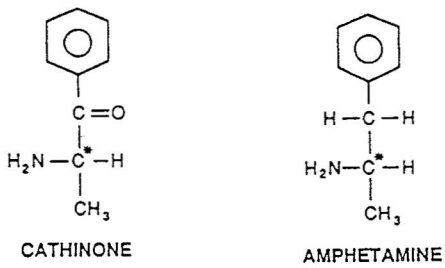
The syndrome that arises from khat consumption consists of a central stimulatory action accompanied by sympathomimetic effects. It is characterized by feelings of

elation and enhanced self-esteem while energy and alertness seem to be increased. The chewer becomes communicative and tends toward social interaction, and may develop ideas of greatness and a latent aggressivity. Objectively, khat consumption induces mild euphoria and excitement accompanied by loquacity or even logorrhea, and the chewer appears increasingly unrealistic and emotionally unstable. Sometimes, there will be manic behavior and hyperactivity (Giannini & Castellani 1982); hypnagogic hallucinations may occur as a corollary (Granek, Shalev & Weingarten 1988). Excessive use of khat can induce psychosis; however, because of the difficulty of taking large quantities of the drug, this reaction is exceptional and probably limited to persons that are particularly sensitive to the effects of psychostimulants. Nonetheless, a number of cases of khat-induced psychosis have been reported in the literature, and these have been compared and discussed in a synopsis by Pantelis, Hindler and Taylor (1989). Since a paranoid reaction can appear, including tendencies to violent behavior, the symptoms may be prominent enough to require treatment. Usually, antipsychotic medication of the phenothiazine type is employed, but haloperidol and diazepam have also been used. Recently, Giannini, Miller and Turner (1992) suggested bromocriptine for the treatment of khat addiction.

The symptoms brought about by khat consumption are reminiscent of those induced by amphetamine. Indeed, Alles, Fairchild and Jensen (1961) and Hughes (1973) have reported after self-experiments that the effects of a portion of khat are much the same as those of a low dose of amphetamine, and Hodgkinson (1962) has given a similar opinion after a series of experiments with khat-experienced Kenyans. This raises the question whether khat also has some dependence potential. Indeed, chronic khat use may be compulsive and can be regarded as a phenomenon of drug addiction; the World Health Organization has come to the conclusion that the habit may give rise to moderate but often persistent psychic dependence (Eddy et al. 1965). However, the withdrawal symptoms that may follow prolonged khat use are minor and they are limited to lethargy, mild depression, nightmares, and slight tremor (Kennedy, Teague & Fairbanks 1980; Halbach 1972).

The systemic effects of khat are reflected by small increases in respiration and body temperature (Nencini et al. 1984); further, khat is an effective anorectic, and its use also results in constipation. The mydriasis that is often prominent during khat consumption reflects the sympathomimetic effects of the drug, which are mainly seen at the cardiovascular level. Accordingly, khat may provoke an increase in blood pressure and heart rate (Drake 1988; Halbach 1972; LeBras & Frétillère 1965), which is less prominent in habitual users and thus reflects the development of a certain degree of tolerance (Nencini et al. 1984). Under the effect of khat, cardiovascular regulation becomes labile and the response to physical effort tends to be excessive (LeBras & Frétillère 1965; Galkin & Mironychev 1964).

FIGURE 1
Chemical Structure of the Khat Alkaloid Cathinone and of Amphetamine



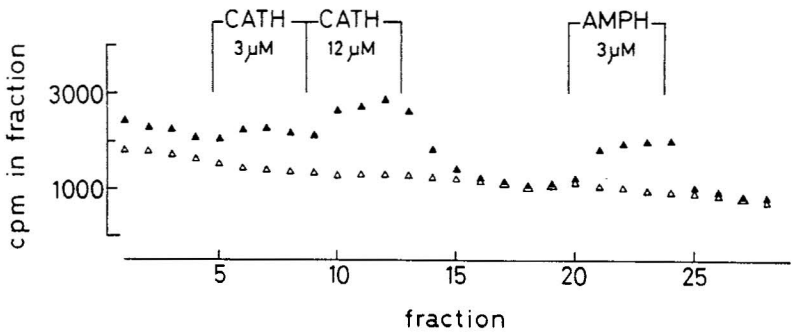
CATHINONE AMPHETAMINE

The acute effects of khat are difficult to quantify because the content of active constituents varies not only from plant to plant, but also depends on the maturity of the leaves as well as on their freshness. There are also interindividual differences regarding the extraction and the absorption of these constituents (i.e., differences in the efficiency of the mastication process). In a recent clinical investigation with volunteers unfamiliar with khat (Kalix et al. 1993), attempts were made to obviate these difficulties by comparing the effects of standarized khat under double-blind conditions to those of a genuine placebo (i.e., to khat from which the active constituents had been removed by extraction). The results of this study provide experimental evidence for the sympathomimetic effects of khat, as well as for the psychostimulant and euphorigenic action that reinforces the practice of chewing this drug.

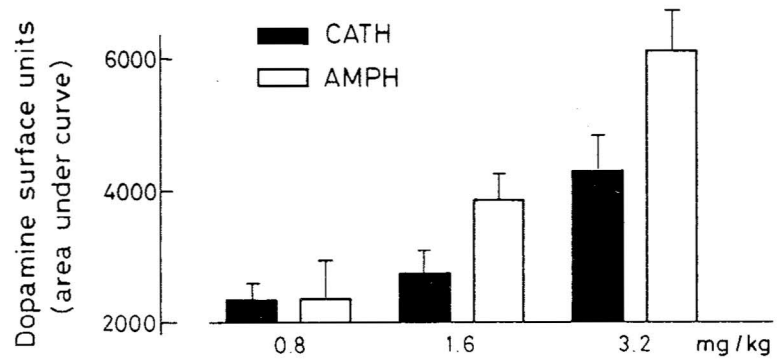
ACTIVE CONSTITUENTS

In the countries where khat use is widespread, its social and medical repercussions are significant problems. In 1958, these were brought before the Economic and Social Council of the United Nations, and twelve years later the United Nations Narcotics Laboratory undertook a reanalysis of the constituents of the khat leaf. These investigations have been described by Szendrei (1980). They were furthered by an analogous project initiated independently at the University of Berne (Schorno & Steinegger 1979), and culminated in the discovery of [–]-s-α-aminopropiophenone, a new alkaloid for which the term "cathinone" was introduced. Structurally, cathinone is closely related to amphetamine, the difference being that cathinone carries a carbonyl group instead of the methylene group in the alpha position of the amphetamine side-chain (see Figure 1).

FIGURE 2
The Effect of Cathinone and of Amphetamine on the Release of Dopamine from Rat Nucleus Accumbens In Vitro (Upper Panel) and In Vivo (Lower Panel)



Upper panel: Efflux of radioactivity from isolated nucleus accumbens tissue prelabeled in vitro with titrated dopamine and superfused with a saline solution in which cathinone and amphetamine were present periodically. The open triangles indicate the efflux from an unstimulated control preparation superfused simultaneously; one fraction corresponds to three minutes. From figure 1 in Kalix (1982).



Lower panel: Release of dopamine in vivo from the nucleus accumbens of rat after intraperitoneal injection of various doses of cathinone and of amphetamine. The concentration of dopamine was determined by microdialysis in situ; column height is proportional to the area under the curve that describes the time course of the extracellular concentration of dopamine in the tissue. Redrawn from figure 2 in Pehek, Schechter and Yamamoto (1990).

The pharmacological screening of the new alkaloid was carried out by a group of advisors to the World Health Organization (1980), and cathinone was soon recognized as being a highly potent central nervous system (CNS) stimulant. In particular, it was noted that the effects of cathinone in animals were analogous to those observed in humans after khat consumption. In the course of these investigations it was found, for example, that cathinone increases the locomotor activity of rodents, and that it causes extreme restlessness and tremor when injected in monkeys. In further experiments conducted with rats that had been trained to distinguish between placebo and amphetamine, it was observed that the response of the animals persisted when amphetamine was replaced by cathinone (Kalix & Glennon 1986; Schechter, Rosecrans & Glennon 1984; Rosecrans et al. 1979), and self-administration studies with monkeys showed that the reinforcing efficacy of cathinone is, under certain conditions, the same as that of cocaine (Woolverton & Johanson 1984). In these experiments, the animals made frequent injections of cathinone during periods of up to several days, then stopping because of exhaustion and starting again after recovery; this pattern of self-administration is typical for abuse of substances of the amphetamine type. In this context, it is of importance that such animals perceive cathinone as being much less aversive than amphetamine (Goudie & Newton 1985).

In order to determine the role of cathinone in the syndrome that is observed in humans after khat consumption, its effects were also assessed through a clinical experiment involving six healthy volunteers (Brenneisen et al. 1990) in which the substance was administered orally in gelatine capsules at a dose corresponding to 100 g khat of average

cathinone content. An evaluation using the questionnaires of the Addiction Research Center Inventory revealed a marked psychostimulant and euphorigenic effect of cathinone, which at the same time caused an increase in blood pressure and heart rate. These changes coincided with the presence of cathinone in blood plasma, its half-life was determined as being approximately 1.5 hours (i.e., as being much shorter than that of amphetamine).

The close resemblance between the effects of cathinone and those of amphetamine implies the possibility that the two compounds have a common mechanism of action; that is, cathinone acts like amphetamine by inducing the release of neurotransmitter at catecholaminergic nerve endings. In order to examine this possibility, experiments were made with isolated rabbit striatal tissue that had been prelabeled with radioactive dopamine. Cathinone was found to induce the release of radioactivity from this preparation (Kalix 1980), and similar in vitro results were obtained with other preparations from the CNS (Wagner et al. 1982; Zelger & Carlini 1981). In particular, it was shown that the dopamine-releasing effect of cathinone also pertains to the nucleus accumbens (see Figure 2, upper panel), a brain structure that is essential for the effect of amphetamine on motor activity. This finding was borne out by in vivo experiments demonstrating that the extracellular concentration of dopamine in the nucleus accumbens increases when the animals receive intraperitoneal injections of either cathinone or amphetamine (see Figure 2, lower panel). Taken together, these observations indicate that the behavioral effects of cathinone are due to an activation of dopaminergic pathways in the CNS, and that they involve the same mechanisms as those of amphetamine. Moreover, this analogy pertains also to the action of the two compounds on peripheral noradrenergic nerve endings mediating sympathomimetic effects. Indeed, cathinone also induces the release of radioactivity from noradrenaline-prelabeled heart tissue in vitro (Kalix 1983a); again, this observation is consonant with the results of in vivo experiments (Kohli & Goldberg 1982). Thus, much experimental evidence indicates that cathinone is, in fact, a naturally occuring amphetamine.

Although the effects that are seen in humans after khat consumption are explained satisfactorily by those of their constituent cathinone, there remains the possiblity that other alkaloids contribute to the khat syndrome. Indeed, the concentration of cathine in the leaves, a substance that is a congener of cathinone and that is also called norpseudoephedrine, is generally superior to that of cathinone (Geisshüsler & Brenneisen 1987), and before the discovery of cathinone this alkaloid was considered to be the main active principle of khat (Alles, Fairchild & Jensen 1961; Winterfeld & Bernsmann 1960). It is now known, however, that the importance of cathine for the stimulatory action of khat is negligible. This is evidenced by the fact that wilted leaves, in which the cathinone content is strongly reduced while that of cathine is unchanged, are not used for chewing. In point of fact, in various animal experiments cathine is much less potent than cathinone, and in release studies with isolated CNS tissue, such as the one described above, cathine has been found to have only one-eighth of the potency of cathinone (Kalix 1983a). Further, because of its lower lipophilicity, cathine is in vivo much less able to penetrate to sites of action within the CNS.

CONCLUSION

The habit of chewing khat is endemic in the countries between Sudan and Madagascar, and in Yemen in particular where it has a deep-rooted cultural tradition. In the recent past, the consumption of this drug has increased sharply, due to the improved transportation and storage of the material and the profound social changes that have occurred in the countries concerned. Emigrants have now brought the khat habit to other parts of the world. Even though the khat session may help them to preserve ethnic identity in a completely new environment, it is worrisome that a drug habit is spreading that may be harmful and involves the risk of dependence. It remains to be seen if khat will suddenly become a fashionable drug among other populations, or if the unattractive mode of consumption acts as a deterrent for those unfamiliar with the habit. In this respect, it would be interesting to investigate the situation in Israel, where khat use has remained sporadic ever since it was introduced some 40 years ago by Jewish immigrants from Yemen, and where there appear to be no noteworthy problems with the drug.

The effects of khat must be seen in the same light as those of amphetamine. However, to a certain extent they are self-limiting: on one hand, the dose that can be taken is limited by the bulkiness of the material while the active constituents must be extracted laboriously by chewing, and on the other hand the main psychoactive alkaloid has a plasma half-life of only 1.5 hours. For these various reasons, it appears likely that there is a limitation to the cathinone plasma level that can be attained by chewing the leaves. These "safety factors" may explain why in some societies the use of khat is an accepted and even respected drug habit, and why khat is tolerated in certain countries where it is illicit. Unfortunately, khat consumption is in certain cases compulsive, which is reflected by the fact that the need for khat may engender small crimes, and that for some users the leaves are more important than certain vital needs, such as food. Still, there seems to be no craving for the drug, despite the use of this term by Theodore Dreiser for the hero of his short story "Khat."

Khat consumption triggers only exceptionally acute health problems, even though these may be severe. However, there are important indirect effects, such as the

anorexia, which—together with the reluctance to spend money on anything other than khat—leads to malnutrition. This predisposes the habitué to infections, among which tuberculosis is a particular threat because the participants of a khat session discharge the chewed residues by expectorating and often smoke collectively from a water pipe. In addition, in those countries where khat is used by a substantial segment of the population, the habit also has important economic consequences. Indeed, the prolonged khat sessions and the subsequent feeling of depletion leave little time for occupational activity, and there is loss of productivity and income not only for the individual, but also for the national economies. This certainly is a relevant factor, because the countries concerned are among the world's poorest. Moreover, the production of khat occupies scarce arable land and requires precious irrigation water that should be used for more useful crops. Thus, khat is a recreational drug the use of which has large implications at the societal level.

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