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REVIEW

THE PHARMACOLOGY OF KHAT*

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INTRODUCTION

The first written account of the habit of chewing leaves of the khat shrub† appeared more than seven centuries ago In *The Book of Compound Drugs*, Naguib Ad Din (as quoted by LeBras and Frétillère, 1965) described khat leaves as a cure for melancholia and depression and indicated their usefulness for easing the atmosphere on social occasions Other authors of the same era recommended khat for alleviating the sensations of hunger and fatigue and suggested the use of khat by soldiers and messengers Today, several million people are frequent users of this stimulant, they live in the countries between Sudan and Madagascar and in the south-eastern part of the Arab Peninsula Khat use has remained confined to the regions where khat is grown, because only the fresh leaves have the desired stimulating effect In recent years, however, the use of khat has expanded considerably Although formerly, the leaves were only available in or close to the areas of cultivation, at present, improved roads, off-road vehicles and particularly the possibility of air transport, allow a much wider distribution of this non-storable commodity

Cultivation and consumption of khat have profound socioeconomic consequences for the countries concerned Scarce arable land and irrigation water are used for growing khat instead of nutrient plants or the export crop coffee (Krikorian and Getahun, 1973) Furthermore, khat chewing results in a considerable loss of man-hours and decreases productivity in terms of both quantity and quality The habit also has a substantial impact on the balance of payments for countries that rely mainly (e g Somalia) or exclusively (e g Djibouti) on khat grown in nearby foreign areas

Of even greater importance is the impact of khat use on the individual Khat users, most of whom are male, frequently harm their families by negligence, dissipation of family income, and by inappropriate behaviour After the chewing of khat, they tend to be either agitated and aggressive, when still under the effect of the drug, or silent and withdrawn when the effect has worn off As an illustration of this problem, there is the estimate that, in Djibouti, about one third of all wages and salaries are spent on khat and that the drug is a factor in one out of two divorces (T Baasher, WHO Eastern Mediterranean Regional Office, personal communication)

The epidemic spreading of khat use has led to an increased interest in the medical aspects of the habit and has resulted in intensified efforts to identify the constituents of the leaves Several years ago, a new alkaloid, (−)cathinone, was isolated from khat This substance was found to be a "natural amphetamine" and largely responsible for the effects observed after khat chewing The purpose of the present report is to describe the khat habit and its effects and, particularly, to survey the pharmacological studies of (−)cathinone, the main constituent of khat

KHAT USE AND EFFECTS

Most descriptions of khat use are based on observations made in Yemen, where khat is consumed predominantly in a social setting The young shoots of the khat shrub (which grows on moist slopes at 3–8000 feet altitude) are harvested in the early hours of the day and sold in markets in the late morning Traditionally, the khat chewers assemble in someone's home at the beginning of the afternoon and slowly consume about 100–200 g of the leaves per person The leaves are taken one by one from the twigs and thoroughly chewed They are then kept for a while in the cheek as a ball of macerated material and later expectorated The young leaves, which come from the tips of the branches, are preferred since these are the most potent Male and female users congregate separately, for male users in particular, the khat session (which usually lasts for 3–4 hr) has an important social function since it provides a forum for discussing matters of general interest such as community affairs The chewers describe the drug as having a number of beneficial effects such as improving their ability to communicate, to generate new ideas and to suppress the feeling of fatigue The social environment appears to influence the response of the chewer, and the effect is said to be more readily perceived by the habitual user Further details regard-

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†*Catha edulis*, *Celastraceae* Khat is known under about 40 names, e g Miraa in Kenya The spelling khat, which is highly debatable for the linguist, has been chosen here because it is by far the most widely used one in the literature

ing the social aspects of khat chewing can be found in the reports of Hughes (1973), Nelhans (1974) and Kennedy *et al* (1980) For the observer, the stimulant effect of the drug can be perceived as a moderate degree of euphoria and excitation often accompanied by logorrhea Higher doses can be seen to induce hyperactivity and, sometimes, manic behaviour Insomnia is a corollary effect of khat use The temporal sequence of the psychic effects of khat has been described by LeBras and Fretillère (1965)

Many habitual khat chewers tend to compulsive use of the drug, and in these users, in particular, the effects may include aggressive behaviour, paranoid ideation and ultimately personality disorders The tendency of these khat chewers to obtain their daily supply of khat at the expense of vital needs is a clear indication of psychic dependence Cessation of the practice may lead to a certain degree of reactive depression (Halbach, 1972) Drug dependence of the khat type has been described by Eddy *et al* (1965) who have stressed the similarity between the effects induced by khat and those caused by amphetamine and Gendron, 1976, Dhadphale *et al*, 1981) Of particular interest is a recent paper (Giannini and amphetamine intoxication is manic psychosis, the question arose as to whether this syndrome can also be induced by khat chewing and this, in fact, has been reported to be the case (Carothers, 1945, Ardouin and Gendron, 1976, Dadphale *et al*, 1981) Of particular interest is a recent paper (Giannini and Castellani, 1982) that reports a case of manic psychosis involving a North African student in the United States, who had grown the khat in his own apartment An important difference between khat and amphetamine must be borne in mind and that is that the intake of khat is self-limiting due to the bulkiness of the material Cases of khat-induced psychosis, therefore, seem to occur only after consumption of exceptionally potent material or in predisposed persons The difficulty of increasing khat intake beyond a certain limit might also explain the fact that no development of tolerance to the CNS-stimulating effect of the drug has yet been reported (see Lemordant, 1966)

Other known effects of khat on the central nervous system are hyperthermia and increased respiration (LeBras and Frétillere, 1965, Halbach, 1972, Nencini *et al*, 1983), impaired motor coordination has also been reported (LeBras and Frétillère, 1965) Khat is also an effective anorectic (Halbach, 1972, Luqman and Danowski, 1976) and this would largely explain the malnutrition generally observed in habitual khat chewers Khat intake does not appear to modify the blood level of glucose (Elmi, 1983)

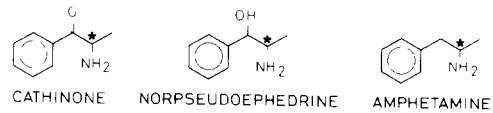
The peripheral effects of khat chewing are of the sympathomimetic type At the cardiovascular level there are arrhythmias and an increase in blood pressure depending on the quantity and potency of the material absorbed (Halbach, 1972, Nencini *et al*, 1983) The cardiovascular response to physical effort is exaggerated (LeBras and Frétillère, 1965) Acute cardiovascular problems, particularly in older people, have been reported (Gendron *et al*, 1977) The habitual intake of khat may result in chronic hypertension, which regresses after cessation of the practice (Halbach, 1972) Other sympathomimetic effects of khat use are mydriasis (Halbach, 1972, Nencini *et al*, 1983) and spermatorrhea (LeBras and Frétillere, 1965, Halbach, 1972) Another frequent symptom due to khat consumption is constipation, but this is probably related to the high tannin content of the leaves The tannins in khat also account for the various irritative disorders of the upper gastrointestinal tract that are common in chronic khat users (Halbach, 1972) and that can also be induced in rats by feeding khat (Maitai, 1977)

A quantitative assessment of the effects of khat use is difficult since the leaves are a non-standardized material the potency of which depends on freshness and origin Indeed, the different types of khat available on the market vary widely in effectiveness and are only defined by the local trade names There would certainly also be large interindividual variations in the efficiency of the mastication process and in the absorption of the active ingredients Nevertheless, a quantification of several somatic parameters (body temperature, respiratory rate, pulse rate and blood pressure) in habitual chewers as compared to naive subjects has been attempted with these difficulties taken into account (Nencini *et al*, 1983) The differences between the effects observed in the two groups indicate that the khat-induced changes seem to be less pronounced in chronic users, which suggests the development of tolerance

ACTIVE CONSTITUENTS OF KHAT

Identification of the active constituents of khat was attempted as early as 1887 when Fluckiger and Gerock isolated from khat leaves an alkaloid that they names katin, although they were unable to identify its structure Their experiments also showed that the plant did not contain caffeine Four years later, Mosso (as quoted by Alles *et al*, 1961) reported that the basic fraction of an aqueous khat extract caused mydriasis when injected into frogs and that it had a stimulating effect on the frog heart It was Wolfes (1930) who, probably working with dried khat, identified Fluckigers katin (then spelled cathine) as (+)norpseudoephedrine This substance was then believed to be the main active principle of khat, an opinion that was still held by Winterfeld and Bernsmann (1960) and Alles *et al* (1961) The conclusions of the latter author were based on experiments on animals and on himself, in which a comparison was made of fresh khat, extract of dried khat and pure (+)norpseudoephedrine The analytical results excluded the presence of amphetamine in khat

It had previously been pointed out, however (Brucke, 1941) that (+)norpseudoephedrine is a stimulant of rather low potency and that the amount of the substance present in a portion of khat is insufficient to account for the symptoms observed after its consumption In an attempt to explain this



CATHINONE NORPSEUDOEPHEDRINE AMPHETAMINE

discrepancy, Friebel and Brilla (1963) investigated extracts of lyophilized fresh khat leaves and were successful in isolating an unidentified alkaloid that

was considerably more potent than (+)norpseudoephedrine in stimulating the motor activity of mice Since this substance, possibly because it is quite labile, could not be detected in dried leaves, it was suggested that the new alkaloid was converted to (+)norpseudoephedrine during the drying process

International organizations were confronted with the problems associated with khat as early as 1935, when the Advisory Committee of the League of Nations on the Traffic of Dangerous Drugs discussed two technical reports on the subject Through the UN 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 UN Narcotics Laboratory reinvestigate the chemical composition of khat The resulting studies (Braenden, 1979, Szendrei, 1980) led to the isolation of the compound S-(−)-α-aminopropiophenone, from khat leaves and the name (−)cathinone was suggested (UN Document, 1975) The configuration proposed for (−)cathinone was confirmed by Schorno and Steinegger (1979) by comparison with the synthetic compound, they subsequently studied the distribution of the alkaloids in fresh khat of various origins and in different parts of the plant (Schorno *et al*, 1982) It was found that in certain khat samples, the phenylalkylamine fraction consisted of up to 70% (−)cathinone and that the (−)cathinone content correlated with the market price of the material It was also concluded that (−)cathinone is probably a biosynthetic intermediate that tends to accumulate in young, but not in adult leaves where it is converted to about 4/5 of (+)norpseudoephedrine and 1/5 of (−)norephedrine Similarly, this conversion occurs rapidly during the drying of young leaves

A number of other constituents have been identified in khat (Cais *et al*, 1975, Baxter *et al*, 1976a,b, Braenden, 1979, Szendrei, 1980, Gellert *et al*, 1981), but these have not yet been pharmacologically assessed It is unlikely, however, that these substances (except for the tannins) contribute to any important extent to the effects of khat, which as will be shown, can be satisfactorily explained by the presence of (−)cathinone

PHARMACOLOGY OF CATHINONE

Once (−)cathinone was recognized as the major active principle of khat leaves, studies were initiated by an advisory group of the World Health Organization (see references Knoll, 1979, Yanagita, 1979, Schuster and Johanson, 1979, Rosecrans *et al*, 1979, WHO Advisory Group, 1980) in order to investigate the pharmacological properties of the new compound In a survey of the effects of (−)cathinone it was found, for example, that injection of 1 mg/kg to anaesthetized rats or cats caused a substantial increase in blood pressure (Knoll, 1979) This was confirmed by Yanagita (1979) who also observed a positive inotropic and chronotropic effect of (−)cathinone in isolated guinea pig heart In these experiments, (−)cathinone was found to have a potency comparable to that of (+)amphetamine The close similarity of the cardiovascular effects of (−)cathinone and (+)amphetamine was confirmed by Kohli and Goldberg (1982) in a subsequent study on anaesthetized dogs During the examination of the effects of (−)cathinone on other organs with prominent sympathetic innervation, it was found that constrictions of the rabbit ear artery induced by low frequency stimulation were potentiated by (−)cathinone and that the potency of the alkaloid was similar to that of (+)amphetamine (Knoll, 1979) This potentiating effect of (−)cathinone *in vitro* might account for the exaggerated cardiovascular responses to physical effort observed after khat chewing (LeBras and Frétillère, 1965) (−)Cathinone was also found to potentiate constrictions of the isolated guinea pig vas deferens induced by electrical stimulation (Knoll, 1979), a finding that may explain the frequent occurrence of spermatorrhea in khat users (LeBras and Frétillère, 1965, Halbach, 1972) Another commonly seen symptom of khat use, mydriasis, has been consistently observed after injection of (−)cathinone to monkeys in the course of behavioural experiments (Schuster and Johanson, 1979, Yanagita, 1979) The flexor reflex of the hind limb of the spinal rat is considered a good model for studying the action of drugs on central noradrenergic neurons In this preparation (−)cathinone is as potent in stimulating the response as (+)amphetamine (Knoll, 1979) Taken together, these findings indicate that (−)cathinone acts by facilitating noradrenergic transmission and accounts for the sympathomimetic syndrome observed after khat consumption

Amphetamine is known to have analgesic effects that can be demonstrated in various experimental models This is also the case for (−)cathinone which increases reaction time in the hot plate test, an effect that, as in the case of amphetamine, is antagonized by inhibitors of catecholamine synthesis (−)Cathinone also shows analgesic properties in the writhing test (Knoll, 1979, Nencini and Ahmed, 1982) The analgesic effect of (−)cathinone was studied in greater detail by Nencini and Ahmed (1982) who, using the tail flick test, found that naloxone could prevent cathinone's effect

With regard to metabolic regulatory mechanisms, it has been found that, in rats, (−)cathinone increases oxygen consumption and metabolic rate (Knoll, 1979), it also increases lipolysis under *in vitro* and *in vivo* conditions (Nencini, 1980) These effects might explain the increase in respiration usually observed in khat chewers (LeBras and Frétillère, 1965, Halbach, 1972, Nencini *et al*, 1983) It has also been suggested that this respiratory effect may be a reaction to the hyperthermia that is known to develop after khat consumption (Halbach, 1972) With regard to this phenomenon, it has been shown that injection of (−)cathinone to rabbits induces hyperthermia (Kalix, 1980a) and this analogy to amphetamine extends to the induction of hypothermia in cold-acclimated animals by (−)cathinone (Kalix, manuscript in preparation)

In some of the studies summarized above, the effects of the (+)isomer of cathinone were also examined and they were generally found to be quantitatively similar to those of the (−)isomer These results, however, are not relevant to the pharmacology of khat, since the plant does not contain the (+)isomer

Table 1

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	
Logorrhea	
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)

There appear to be no published data on the pharmacokinetics of (−)cathinone, according to Schorno (personal communication), (−)cathinone is metabolized mainly during the first liver passage and only a very small fraction appears in the urine along with (−)norephedrine, the principal metabolite (+)Norpseudoephedrine, on the other hand, has been reported to be excreted in the urine mainly unchanged (Maitai and Mugera, 1975) There are, however, also experiments indicating that *in vitro*, (+)norpseudoephedrine can be converted by dopamine-β-hydroxylase into (−)cathinone under conditions that suggest physiological relevance (May *et al*, 1982) This finding evokes the possibility that, *in vivo*, (+)norpseudoephedrine functions as a (−)cathinone precursor and this idea is supported by the fact that (+)norpseudoephedrine has a delayed onset and long duration of action

BEHAVIOURAL EFFECTS OF CATHINONE

Since the main effect of khat is CNS stimulation, a number of studies have been made of the effects of cathinone on animal behaviour and on locomotor activity in particular Pronounced restlessness, observed in monkeys after administration of racemic cathinone, was quantified by measuring the locomotor activity of rats after s c injections of the substance (Yanagita, 1979) The results showed that cathinone was almost as potent as (+)amphetamine in inducing hypermotility Similar results have been reported for mice (Knoll, 1979) Zelger *et al* (1980) compared the effects of racemic cathinone, and those of (+)norpseudoephedrine, on the locomotor activity of mice as a function of time The time course of cathinone's effect was found to be similar to that of (+)amphetamine, that of (+)norpseudoephedrine, which was found to be a less potent substance, showed a slower onset of action but a longer-lasting effect Close similarities between (−)cathinone and (+)amphetamine were also observed when the effects of the two substances on locomotor activity were compared in hypophysectomized and non-operated rats (Kalix, 1980b) In another study using mice (Valterio and Kalix, 1982) it was demonstrated that (−)cathinone's effect on locomotor activity is characterized by a dose–response curve of inverted-U shape (i e the response diminishes when the dose is increased beyond a certain level), which is typical of stimulants of the amphetamine type Taken together, the results of these studies indicate that (−)cathinone induces hypermotility in rodents in a way similar to that induced by (+)amphetamine, that its potency is similar to that of (+)amphetamine and considerably higher than that of (+)norpseudoephedrine

Several studies have been made of the effect of antagonists on the locomotor response to (−)cathinone It has been reported that this response was only partially abolished by prior reserpinization of the test animals (Knoll, 1979), a finding that was confirmed by Valterio and Kalix (1982) and which corresponds to a known characteristic of (+)amphetamine hypermotility (Ross, 1979) In an attempt to determine whether, as in the case of (+)amphetamine, the stimulation of locomotor activity involves activation of dopamine receptors, the effect of (−)cathinone was studied in mice pretreated with substances known to antagonize the postsynaptic effects of dopamine It was found that, at concentrations relevant for dopamine antagonism, haloperidol, spiroperidol and pimozide blocked the locomotor response to (−)cathinone (Valterio and Kalix, 1982), which is in agreement with findings regarding the response to (+)amphetamine (Tseng and Loh, 1974, Roberts and Fibiger, 1975) The response to (−)cathinone was also found to be inhibited by substances with stereospecifically determined antagonistic properties, i e the active isomers of butaclamol and flupentixol (Fig 1)

(−)Cathinone has also been found to be similar to (+)amphetamine with regard to induction of stereotypical behaviour (Zelger *et al*, 1980, Peterson *et al*, 1980, Kalix, 1980a) In one study (Glennon and Showalter, 1981), however, no stereotypical activities were observed in mice after injection of 17 mg/kg (−)cathinone, a dose found by others (Valterio and Kalix, 1982) to consistently cause such behaviour in the same species Zelger *et al* (1980) evaluated several parameters of stereotypical behaviour induced in rats by racemic cathinone (20 mg/kg) as well as the effect of certain antagonists They observed that the overall effect of cathinone was very similar to that of (+)amphetamine, but not to that of the dopamine receptor agonist apomorphine, which suggested the conclusion that cathinone acts at the presynaptic

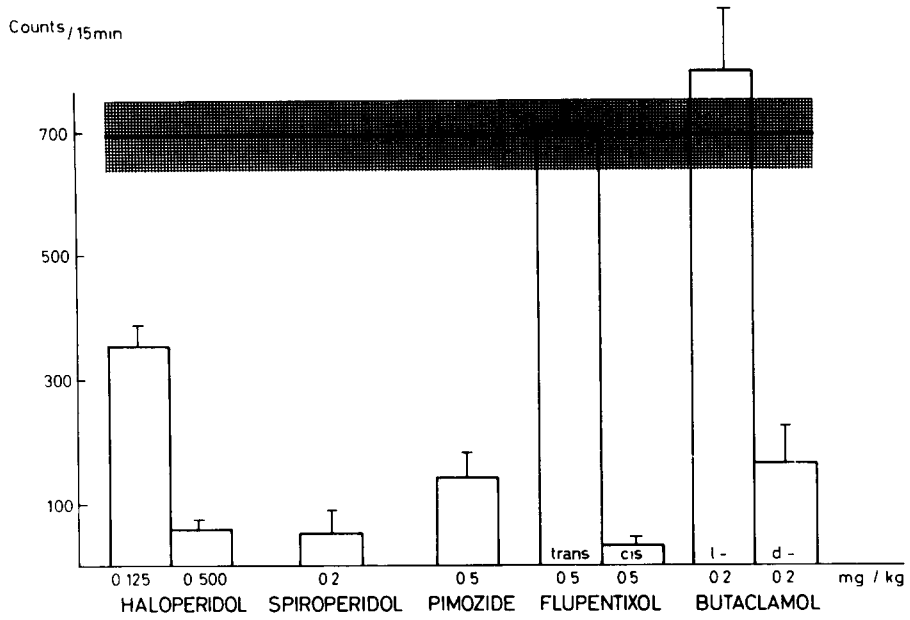


Fig 1 The effect of antagonists on the (−)cathinone-induced locomotor activity of mice The substances were injected 45 min (pimozide 3 hr) prior to administration of (−)cathinone The shaded area indicates the effect of the same dose of (−)cathinone (18 mg/kg) without pretreatment, the locomotor activity of saline-injected animals was 229 ± 91 counts/15 min (From Valterio and Kalix, 1982)

level (+)Norpseudoephedrine induced the same type of stereotypical behaviour as did cathinone, but was only about one fourth as potent A further indication of the similarity of the CNS stimulation caused by cathinone and amphetamine is given in a study of the effects of these two substances in rats with unilateral lesions of the substantia nigra (Zelger and Carlini, 1981) In such animals, direct dopamine agonists (e g apomorphine) induce contralateral rotational behaviour, while drugs with indirect action cause ipsilateral rotations This latter effect was in fact observed for racemic cathinone, which was found to be about half as potent as (+)amphetamine The effect of (+)norpseudoephedrine was similar but longer lasting, and this substance was about one fourth as potent as cathinone These findings suggest that the mode of action of the khat alkaloids is the same as that of amphetamine

For many centuries khat leaves have been used, not only as a stimulant, but also to alleviate the sensation of hunger An anorectic effect of the alkaloid cathinone was observed in the course of behavioural experiments on monkeys (Yanagita, 1979) and analogous observations were made in rats (Knoll, 1979) Similarly Zelger and Carlini (1980) found that treatment of rats with cathinone resulted in reduced food intake of the animals and eventually decreased body weight This was also true, although to a considerably lesser extent, for (+)norpseudoephedrine On the other hand, cathinone was found to be a less potent anorectic than amphetamine The effect of cathinone was characterized by development of tolerance, which occurred almost twice as rapidly as in the case of amphetamine Furthermore, cross tolerance of the effects of the two stimulants was observed In a study of the effectiveness of racemic cathinone and (+)amphetamine in decreasing milk intake of rats (Foltin and Schuster, 1982), cross tolerance was also observed It was found that tolerance caused a dose–response curve shift by a factor of 8–12 for cathinone and only of 2 for (+)amphetamine Another substantial quantitative difference between the two compounds was observed during evaluation of their effectiveness in inducing gustatory avoidance conditioning, a behavioural effect of many psychomotor stimulants In this paradigm, cathinone was found to be considerably less potent than (+)amphetamine (Foltin and Schuster, 1981)

In studies of the effects of cathinone and (+)amphetamine on operant behaviour, the two compounds were also found to be very similar Thus, the effects of cathinone closely resembled those of (+)amphetamine with regard to modification of food-maintained behaviour in rats (Yanagita, 1979) and rhesus monkeys (Johanson and Schuster, 1981) Another important finding concerning the effectiveness of cathinone in determining behaviour was that of Rosecrans *et al* (1979) showing that cathinone could be substituted for (+)amphetamine in rats trained to distinguish between a placebo and (+)amphetamine When this substitution was made, the animals responded as if they had been given (+)amphetamine Studies of the self-administration behaviour generated by (−)cathinone illustrate the role of this alkaloid as the dependence-producing constituent of khat leaves In monkeys trained to lever-press for cocaine injections, (−)cathinone functions as a reinforcer and maintains very high rates of responding (−)Cathinone was found, in fact, to be even more potent in this respect than (+)amphetamine (Schuster and Johanson, 1979) Similar results were obtained by Yanagita (1979), who tested the reinforcing capacity of (−)cathinone in monkeys by using the progressive-ratio paradigm With this pro-

cedure, it was determined that the maximal ratio values for self-administration of (−)cathinone were roughly half of those found for cocaine 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

In summary, (−)cathinone can be considered a potent amphetamine-like compound and to be the constituent of khat which is mainly responsible for its CNS effects (+)Norpseudoephedrine has effects similar to those of cathinone, but is less potent Of particular importance is the finding that (−)cathinone enhances behaviour resulting in the availability of the substance to the test animals and can therefore be considered to be the dependence-producing constituent of khat

MECHANISM OF ACTION OF CATHINONE

The cellular and subcellular effects of (−)cathinone were first studied by Rosecrans *et al* (1979), who observed that (−)cathinone, given to mice at a dose of 8 mg/kg, had little effect on brain noradrenaline turnover, but increased that of dopamine significantly, although to a lesser extent than (+)amphetamine Furthermore, *in vitro* experiments with rat striatal slices (Zelger and Carlini, 1981) demonstrated that racemic cathinone could inhibit the accumulation of tritiated dopamine by the tissue Fifty percent inhibition was observed at a cathinone concentration of 3×10^{-6} M, as compared to 6×10^{7} M for (+)amphetamine and $2\,5 \times 10^{-5}$ M for (+)norpseudoephedrine

Among the several distinct effects of (+)amphetamine on dopaminergic neurotransmission, induction of dopamine release is considered the most important (Groves and Rebec, 1976) The question arose as to whether this was also the case for (−)cathinone, since it has been reported to have no agonist action at dopamine receptors (Rosecrans *et al*, 1979) In order to investigate this, the effect of (−)cathinone on the efflux of radioactivity from isolated rabbit caudate nucleus prelabelled with [^{3}H]dopamine was examined (Kalix, 1980c) It was found that superfusion of the tissue with 4 μM (−)cathinone resulted in a rapid and reversible increase of the efflux of radioactivity The amplitude of this effect was approx 60% of that produced by superfusion with the same concentration of (+)amphetamine, whereas (+)norpseudoephedrine had no effect at this concentration (Fig 2) These findings were confirmed by Zelger and Carlini (1981), who showed that in [^{3}H]dopamine prelabelled rat striatal slices racemic cathinone had, at 5 μM, about 2/3 of the effectiveness of (+)amphetamine in inducing the release of radioactivity and that at 50 μM the two compounds were almost equipotent This releasing effect of cathinone *in vitro* correlates with *in vivo* results showing that chronic high-dose treatment of rats with cathinone results in a significant depletion of dopamine from the caudate, telencephalon and midbrain (Wagner *et al*, 1982) The concept that (−)cathinone acts like (+)amphetamine on dopaminergic transmission is also supported by electrophysiological data showing that (−)cathinone, systemically administered to rats, reduces the firing rate of certain neurons in the substantia nigra (Mereu *et al*, 1983) This effect had been previously reported for (+)amphetamine and is thought to be due to striatal dopamine release initiating striato-nigral inhibition (Bunney and Aghajanian, 1976)

The initial findings on rabbit caudate nucleus were extended in further investigations, which showed that the releasing effect of (−)cathinone was perceptible at concentrations below 1 μM More important, the effect was found to be pharmacologically analogous to that of (+)amphetamine, since it could be blocked by preperfusing the tissue with cocaine (Kalix, 1981) and other substances that inhibit dopamine uptake (Fig 3) Since (−)cathinone is known to cause hypermotility of the amphetamine type, it seemed pertinent to examine the effect of (−)cathinone on the release of radioactivity from [^{3}H]dopamine prelabelled tissue of the nucleus accumbens, a region of the brain essential for amphetamine-induced locomotor activity (Kelly and Iversen, 1976) In this tissue, a substantial release of radioactivity could be induced by (−)cathinone, like (+)amphetamine, at a concentration of 3 μM (Kalix, 1982) The same tissue was used for comparing the potency of (−)cathinone with that of (+)norpseudoephedrine with regard to release induction and it was found that in order to reproduce the effect of a given dose of (−)cathinone,

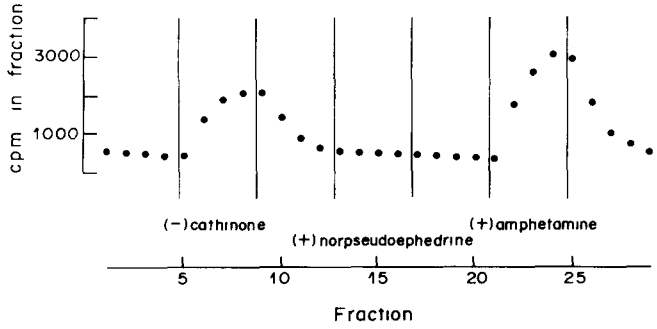


Fig 2 The effect of (−)cathinone, (+)norpseudoephedrine and (+)amphetamine, at a concentration of 4 μM, on the release of radioactivity from isolated rabbit caudate nucleus prelabelled with [^{3}H]dopamine Each fraction corresponds to 3 min of efflux (From Kalix, 1980c)

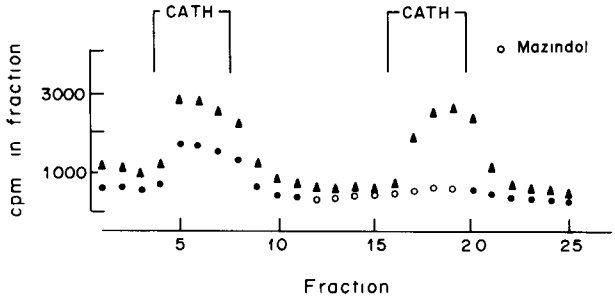


Fig 3 The effect of mazindol on the (−)cathinone-induced release of radioactivity from slices of rabbit caudate nucleus prelabelled with [^{3}H]dopamine Two preparations from the same animal were perfused in parallel and stimulated twice with 10 μM (−)cathinone during 12 min Before and during the second stimulation the test preparation (●) was perfused for 24 min (○) with 1 μM mazindol The efflux from the control preparation is indicated by triangles, each fraction corresponds to 3 min (From Kalix, 1982)

eight times the concentration of (+)norpseudoephedrine was required (Kalix, 1983a)

It can be concluded from the results of these studies that induction of release at CNS dopamine terminals can be considered the mechanism of action of (−)cathinone The potency of (−)cathinone, with regard to this release induction, is comparable to that of (+)amphetamine The effect of (−)cathinone is pharmacologically analogous to that of (+)amphetamine, and occurs in brain areas mediating amphetamine effects This suggests that, in terms of pharmacology, the use of the stimulant khat is tantamount to the use of amphetamine

Since the cardiovascular side effects of khat consumption are of the sympathomimetic type, it seemed of interest to investigate whether the releasing effect of (−)cathinone would also occur at noradrenergic nerve endings In experiments with [^{3}H]noradrenaline prelabelled rabbit atrium tissue, this was in fact found to be the case (Kalix, 1983b) Again, the effect of (−)cathinone was of the same order of magnitude as that of (+)amphetamine and could be modified by the same pharmacological procedures as that of (+)amphetamine, for example, rapid development of tachyphylaxis was seen in tissue obtained from reserpinized animals Furthermore, the releasing effect could be blocked by preperfusing the tissue with desipramine or cocaine (Kalix, 1983b), and it was shown that the efflux inhibition caused by cocaine was unrelated to its local anaesthetic properties (Fig 4)

In rabbit atrium, (−)cathinone has been found to enhance release at concentrations as low as 0 12 μM (Kalix, 1983b), indicating that it is more potent in this respect at peripheral noradrenergic nerve endings than at central dopamine storage sites The other khat alkaloid (+)norpseudoephedrine, however, was found to have, in rabbit atrium, a releasing effect equal in potency to that of (−)cathinone (Kalix, 1983a) Thus, considering their effectiveness at the cellular level, both substances might be said to contribute equally to the peripheral effects of khat chewing *In vivo*, however, the factor of distribution probably plays an important role, since the greater lipophilicity of (−)cathinone favors its penetration into the CNS It must also be borne in mind that the proportion and absolute content of the two alkaloids in khat leaves can vary considerably (Schorno *et al*, 1982)

CONCLUDING REMARKS

The chewing of khat, which probably antedates the use of coffee (Heacock and Forrest, 1974), is deeply rooted in the sociocultural traditions of several countries, where it was practiced by a limited segment of the population in a well-defined and stable social setting In recent years, however, the use of this

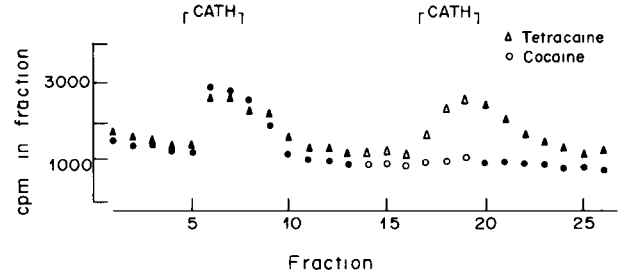


Fig 4 The effect of cocaine and tetracaine on the (−)cathinone-induced release of radioactivity from rabbit atrium tissue prelabelled with [^{3}H]noradrenaline Two preparations (●, ▲) were perfused in parallel and stimulated twice with 1 μM (−)cathinone during a 9 min period Before and during the second stimulation the superfusion medium contained, for an 18 min period, either 8 μM cocaine (○) or 40 μM tetracaine (△) Each fraction corresponds to 3 min of efflux (From Kalix, 1983b)

stimulant has expanded beyond these boundaries and has now reached epidemic proportions This phenomenon can be explained not only by the advent of modern transportation, but also by the profound social and cultural changes that have taken place in these countries in the twentieth century

Pharmacological studies indicate that khat must be considered an amphetamine-like material The khat alkaloid (−)cathinone, which has been shown, in animals, to produce effects similar to those observed in humans after khat chewing, has a pharmacological profile that closely resembles that of (+)amphetamine Of particular importance are the facts that (−)cathinone produces behavioural effects analogous to those of (+)amphetamine and that it induces, like (+)amphetamine, release from physiological catecholamine storage sites

Immediate and severe medical problems arising from khat consumption are infrequent, probably because the (−)cathinone is "diluted" in the bulk material of the leaves from which it is difficult to extract Nevertheless, khat use does constitute a health problem, and this, taken together with the serious socioeconomic consequences of the habit, makes its limitation desirable The application of control measures, however, might be difficult due not only to the wide social acceptance of the habit, but also to the fact that the plant can be found wild-growing in some areas of the countries concerned

It is now known that the effects of khat chewing are mainly due to the pharmacological properties of (−)cathinone, and the finding that (−)cathinone is a potent amphetamine-like compound indicates that there is a certain degree of danger associated with khat use However, as in the case of other drugs of abuse, the problem is less the drug itself than man's need for drugs

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