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Pharmacological Aspects of the Chewing of Khat Leaves

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I. Introduction

In certain parts of eastern Africa and southern Arabia, the stimulating properties of the leaves of the khat bush were probably known before those of coffee (55), and the habit of khat chewing has been common in those areas for many centuries. The effects of khat were reported in the literature as early as 1237 by the Arabian physician Naguib Ad Din (87), who proposed the use of khat for the treatment of depressive states, and by other writers of the same period who reported that it was effective in blunting the sensations of hunger and fatigue (82, 87).

Since the khat leaf rapidly loses its effect upon wilting, the khat habit has remained, until recently, endemic to the areas where the plant was grown. During the last decades, however, due to the development of road networks and the availability of air transport, the habit has spread considerably in those regions and to countries where the plant does not grow. Thus, shipments of khat have even been observed by customs authorities in France, Great Britain, and the United States.

The growing use of khat has motivated an interest in further knowledge of its active ingredients and their pharmacological effects. A number of studies have therefore been made in an attempt to throw light on these problems. The investigations led to the discovery of the alkaloid (−)cathinone, which is now considered to be the constituent that is mainly responsible for the stimulating properties of khat leaves. The present review is intended to describe the medical aspects of khat chewing, to summarize the pharmacological data concerning khat constituents that have thus far been reported in the literature, and to provide some background information.

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II. The Habit of Chewing Khat

In some countries where the use of khat is widespread, the habit has a deep-rooted social and cultural tradition (78, 82, 114a, 121a). This is particularly true for Yemen, where many houses have a room called a muffraj that is specially arranged for regular sessions of khat chewing. In the Yemen Arab Republic, more than 4% of the arable land is used for khat cultivation (115); the bush grows on moist slopes at altitudes of 3000 to 8000 ft, and it is quite adaptable to varying ecological conditions (83, 115). The first khat crop is ready for harvesting 3 to 5 yrs after planting and, although there are marked seasonal differences in regrowth, khat can be harvested throughout the year. The shoots at the tips of the branches are cut in the early hours of the day, bundled, and then usually wrapped in banana leaves to preserve their freshness. The material is then speedily transported to the markets, where it is sold by late morning. The buyer selects from among various types of khat available, which also vary considerably in price, the most expensive (because the most potent) material being, in general, the freshest and that with the youngest leaves.

For the consumption of khat in the traditional social setting, the chewers meet in a house some time after noon, usually bringing their own supply. After being welcomed and carefully seated according to their social position, the guests begin to masticate the leaves thoroughly one by one. The juice is swallowed, while the residue of the leaves is stored in the cheek as a bolus of macerated material for further extraction, and is finally ejected. Altogether, each person takes some 100 to 200 g of the leaves; young leaves are most favored, mainly because they are more potent but also because they are more tender to chew. During the session, the group may smoke from water-pipes, and there is a generous supply

of beverages (65, 89). After the khat leaves have been chewed, the guests stay on for most of the afternoon, passing their time in animated discussions often devoted to matters of general interest, such as community affairs. From this point of view, khat can be seen as a factor furthering interaction and structuring social life. The khat session also plays an important role at weddings and other family events (121a). Khat is frequently used during work by craftsmen, labourers, and especially by farmers, in order to reduce physical fatigue (83). Besides these traditional forms of consumption, khat is nowadays also chewed by single individuals idling in the streets, particularly in towns and cities where it has been introduced within the last decades. In these regions, khat is also consumed (sometimes along with alcoholic beverages and other drugs) at gatherings which lack the restraint and well-defined social setting described above. The social aspects of khat use are discussed extensively in the publications of Hughes (65), Kennedy et al. (78), Nelhans (102), and Schopen (121a).

III. The Effects of Khat Chewing

During the first part of a khat session, there is an atmosphere of cheerfulness characterized by optimism, high spirits, and a general sense of well being. The excitement brought about by the consumption of khat reduces social inhibitions and causes loquacity. After about 2 h, a certain degree of tension that reflects emotional instability and irritability becomes apparent. The talking becomes louder, less relevant to the subject under discussion, and there is a greater awareness of problems. Later, depressive tendencies appear, and a mood of sluggishness prevails. At this point, the guests leave the khat session with a feeling of depletion (6, 54, 87, 95, 113).

The desirable effects of khat leaves, as perceived by experienced users, are relief from fatigue, increased alertness and energy levels, feelings of elation, improved ability to communicate, enhanced imaginative ability and capacity to associate ideas, and heightened self-confidence. These effects seem to be more readily perceived by the habitual user (87). Since the social environment in which the drug is consumed appears to play a role in the response, it is important to take into account not only the effects of khat itself, but those of the khat session as well. It is of interest that the response appears also to be influenced by conditioning, since in Djibouti, where khat is flown in daily, it is commonly said that the effects of the drug begin when the incoming plane is heard in the sky.

The objectively observable effects of khat use consist of mild euphoria and excitement accompanied by episodes of logorrhoea and then verbal aggressivity. There is also an increased sensitivity to sensory stimulation (95); excessive khat use may cause hyperesthesia (58). Hyperactivity may be observed, and the associated behavioral syndrome can be described as hypomania (95); a manifestation of irresponsible fearlessness has also been reported (60). In exceptional cases, khat consumption may produce an immediate dysphoric reaction which might, however, be due to excessive expectations with regard to the potency of a given batch of khat. The late effects of khat use are mainly an inability to concentrate, and insomnia (54, 87). It is important to note that high doses of khat or exceptionally potent material can induce psychosis, presumably by enhancing a subacute prepsychotic or psychopathic condition. However, such symptoms are mentioned only occasionally in the literature, probably because in many cases they are considered as being at the extreme limit of normal behavior. Nevertheless, a number of case reports on khat-induced toxic psychosis have appeared (4, 23, 26, 41, 50, 58). The usefulness of phenothiazines for reducing the central nervous system (CNS) toxicity of khat was reported some time ago (88); at present, thioridazine is suggested for the symptomatic treatment of khat psychosis (50). Impairment of mental health may also be the result of long-term khat consumption; long-term chronic users may develop personality disorders and suffer mental deterioration.

The symptoms described above, particularly that of toxic psychosis, are reminiscent of those induced by amphetamine. Similarity of effects of the two drugs has already been reported, and it has been concluded that the differences between the effects are essentially quantitative (27, 60, 116, 140). Indeed, Hughes (65) has stated from personal experience that the effect of a portion of khat is very similar to that of about 5 mg of amphetamine. A further analogy with amphetamine is that the habitual use of khat is in many instances compulsive, as indicated by the tendency of the chewers to secure their daily supply of the leaves at the expense of vital needs. Drug dependence of the khat type has been described by Eddy et al. (27), and it appears that its only major difference from amphetamine-type dependence is the physical impossibility of increasing the ingested dose beyond a certain limit. This probably explains why tolerance to the psychostimulant effect of khat has not as yet been observed (84, 85, 88). Similarly, no clear abstinence syndrome has been found to occur after prolonged khat use, although a mild depressive reaction during withdrawal from khat is sometimes seen (54, 89). Any definitive investigation of tolerance or withdrawal symptoms would, however, require a thorough clinical study involving monitoring of the blood levels of the active khat constituents.

An important effect of khat, the induction of anorexia (54), was already reported in the early Arab literature. This anorexia, along with the tendency of habitual khat users to divert their funds from food to khat, would account for the generally observed malnutrition which predisposes the users to disease. Ingestion of the leaves seems to have no effect on the blood level of glucose

(refs. 29 and 87; W. H. Peters, unpublished experiments). On the other hand, khat has been reported to cause an increase in respiration and induction of hyperthermia (54, 87, 105); a case of lethal hyperthermia following khat consumption has been described (58).

Consumption of khat, like that of amphetamine, causes a number of sympathomimetic effects. At the cardiovascular level, there are arrythmias and an increase in blood pressure depending on the amount and potency of the material absorbed (54, 105). The cardiovascular response to physical effort is exaggerated (38, 87). Acute cardiovascular problems, particularly in older people, have been reported (40). Habitual use of khat may lead to chronic hypertension which, upon abstinence from the drug, can change into a transient hypotensive state (54). A further sympathomimetic reaction to khat use is mydriasis (54, 95, 105). Khat chewing is known to seriously impair male sexual function and to lead to a high incidence of spermatorrhea which is sometimes accompanied by testicular pain. Long-term chronic use may lead to permanent impotence (54, 87, 95).

Dryness of the mouth is commonly felt during khat chewing (87, 95), and this may be explained either by the sympathomimetic effect of the drug or by its astringent taste. Since khat leaves have a high tannin content, khat chewing frequently causes periodontal disease, mucosal lesions, and a number of irritative disorders of the upper gastrointestinal tract (54, 65, 89, 94). The polyphenolic tannin compounds in khat can also be presumed to increase the probability of oesophageal cancer (99, 122). In an epidemiological field study in Yemen, Kennedy et al. (79), while having the general opinion that the role of khat in the health problems of that country has been highly exaggerated, have nevertheless confirmed the high incidence of gastrointestinal problems in khat users. [In animal experiments, gastritis and duodenitis have been provoked by adding khat or khat extracts to the food pellets of rats (90); on the other hand, inclusion of khat in rat standard diet has been reported to prevent the induction of gastric mucosal damage by phenylbutazone (3), an effect tentatively attributed to the flavonoids present in the leaves (132).] A common ailment of khat users is constipation, probably caused by the astringent properties of the khat tannins. Habitual users try to attenuate this undesirable effect by food adaptation (65), notably by eating, prior to the khat session, a meal with high fat content in order to facilitate intestinal transit (6).

Due to the fact that the leaves are a non-standardized material, the potency of which may vary considerably from batch to batch, it is difficult to make a quantitative evaluation of the effects of khat use. A further problem for clinical studies is the impossibility of replacing the active drug with an indistinguishable placebo. In addition, there are certainly large inter-individual variations in the mastication efficiency and in the absorption of the active ingredients. Although there is, at present, no assay that allows the determination of serum concentrations of active khat constituents, an attempt has been made to determine the effects of khat on several clinical parameters (body temperature, respiratory rate, pulse rate, and blood pressure) in habitual users, on the one hand, and in subjects unaccustomed to khat chewing, on the other (105). The khat-induced changes appeared to be less pronounced in chronic users, which would indicate that tolerance may develop to the sympathomimetic effects of khat. In a short report by the same authors (108), khat chewing is described as causing the same modifications of the plasma levels of somatotropic and adrenocorticotropic hormones as amphetamine.

The mutagenic potential of khat has been estimated in an animal study, in which khat extracts were administered to rats; unfortunately, the i.v. instead of the intragastric (i.g.) route of administration was chosen for these experiments. Under these conditions, the extracts were found to reduce nucleic acid synthesis in brain and liver, and to produce chromosomal abnormalities in bone marrow (25).

IV. Epidemiological Aspects of Khat Use

At present, it is estimated that several million people are frequent users of khat, living in countries between Sudan and Madagascar and in the southwestern part of the Arabian Peninsula. The cultivation and consumption of khat has profound social and economic consequences for the areas concerned. The khat plantations occupy scarce arable land, and they compete, for example, with coffee for the well-irrigated terraces (83). In the rural areas of Yemen, the habit of chewing khat is acquired within the family, usually at an age of between 10 and 14 yr, whereas in urban areas, khat use is usually the result of peer group influence, and abstention can lead to social isolation (7).

An estimation of the prevalence of the khat habit in Yemen was made by two physicians working from 1955 to 1967 in a Yemen municipal hospital (93). Based on data for 27,410 subjects, they found that 60.26% of the males and 34.91% of the females were khat users who had chewed daily for long periods of their life, whereas 30.43% of the males and 23.63% of the females chewed only on holidays or special occasions. It should be mentioned that the traditional form of khat consumption in Yemen involves only male users; khat chewing among women follows a different pattern. Their sessions are less formal and less frequent, and not all of the participants actually chew khat. In general, khat use seems to be less appealing to women than to men. In another survey (4a), that was conducted in several northern Yemen cities among students between 17 and 21 yr of age, it was found that, although only 12% chewed khat, 90% of the students indicated that their fathers used khat, and 60% said that their mothers did so.

In Saudi Arabia, the cultivation and consumption of

khat are forbidden, and the ban is strictly enforced. Through generous crop substitution programs, it has been possible to practically eliminate the cultivation of khat. The ban on khat is further supported by the clergy on the grounds that the Qur'an forbids anything that is harmful to the body. This position is in contrast to that of the church in Yemen, which appears to be divided on the issue and has a generally permissive attitude.

The situation prevailing until recently in Somalia has been analyzed by Elmi (28), who interviewed 7485 randomly chosen subjects living in either the capital Mogadishu or in Hargeisa, a town near the area of khat cultivation. In Mogadishu, 18.26% were habitual users, 20.91% occasional users, and 60.83% did not use khat at all; the respective figures for Hargeisa were 54.96%, 29.26%, and 15.78%. Khat was used by all adult age groups; the incidence of khat chewing was particularly high among businessmen and the unemployed, and it was remarkably low among students. Since then, however, the Somali government has started an energetic campaign against khat use and has banned its importation.

In Kenya, khat chewing is a regional phenomenon, with the two centers of consumption being Nairobi and the Meru district, in which khat is cultivated extensively in the foothills of Mount Kenya. Statistics on production and consumption are not available, but it is known that, until recently, Kenya exported annually quantities of khat valued at approximately 2 million United States dollars (91).

In Ethiopia, khat is widely grown in the Harrar district (83), not only for local use but also for export which now provides about 16 million United States dollars per yr to the national economy. Khat chewing is also common in other parts of the country, and it is practiced by high school and university students as well as the general population (ref. 145; E. Seyoum and Y. Kidane, manuscript in preparation).

In Djibouti, in particular, khat consumption is a luxury habit since the material cannot be grown in that country and has to be imported. Due to a special sales tax, khat trade, although controlled by a private corporation, accounts for about 10% of the government's revenue. On the other hand, the large scale importation of the drug has a considerable impact on the national balance of payments. Mainly because of its ready availability, khat is used, either daily or occasionally, by about 90% of the men and 10% of the women in Djibouti (7). It is estimated that about one-third of all wages is spent on the purchase of khat, while some 8% of the population derive income from khat trade and transport (7).

Among the various consequences of khat use are absenteeism and decreased productivity frequently leading to unemployment. Furthermore, the purchase of khat puts a strain on family income, and the detrimental social effects of the khat habit are felt mainly within the family. The interaction with the father is adversely affected, since he is irritable and quarrelsome while under the effect of the drug, or silent and withdrawn when the effect has worn off. Through its effect on the male reproductive system, the drug leads to progressive estrangement between husband and wife. Thus, the drug has been estimated to be a factor in one out of two divorces in Djibouti (7).

Mainly because of the social and economic problems associated with khat use, international organizations became concerned with this issue as early as 1935. At that time, the Advisory Committee of the League of Nations on the Traffic of Dangerous Drugs discussed two technical reports on the subject (86), but no further action was taken. In 1956, the question was raised during a session of the United Nations Commission on Narcotic Drugs, and the Commission later recommended that the United Nations' Economic and Social Council invite the World Health Organization to study the medical aspects of the habitual chewing of khat (136). The World Health Organization then began to collect relevant data, from which it could be seen that a reinvestigation of the active constituents of khat was necessary for a rational study of the plant's effects.

V. The Khat Plant and Its Constituents

Khat‡ is cultivated as a bush or, as in Kenya, as a small tree that is kept low by pruning. Wild growing trees may reach 25 m in height, as in the case of the so-called Chirinda Redwood of Zimbabwe (50a). The khat plant is highly polymorphic, and the branches have either opposite or alternate leaves (50a, 109). These are 1 to 4 cm wide and 5 to 10 cm long, they have a serrated edge, and their shape ranges from elliptical to lanceolate. They are brownish-green and somewhat leathery, their upper surface is glossy, the odor is faintly aromatic, and the taste is astringent and slightly sweet (109, 127). The short round petioles and the stems are of a colour that varies from whitish to red. Since the plant has no unique morphological or anatomical features (2, 110, 127), its unequivocal identification must rely on chromatographic methods (110). A rapid and simple means of identifying the leaves would be of great value to law enforcement authorities. It would also be useful to direct efforts towards establishing a thorough taxonomy of the genus Catha. Indeed, different commercial types of khat are only distinguished by their local trade names (see, e.g., refs. 113 and 121a). In this context, mention must be made of a particular type of khat that comes from Kenya and that consists of young sprouts growing out of the stems of the major branches; with this type, which is particularly potent, the whole stalk is chewed, since its bark is also active.

The question of the active principle of the khat plant

‡ Catha edulis, Celastraceae. The plant is known under a great variety of names (e.g., Miraa in Kenya) among which "khat" is the most widely used.

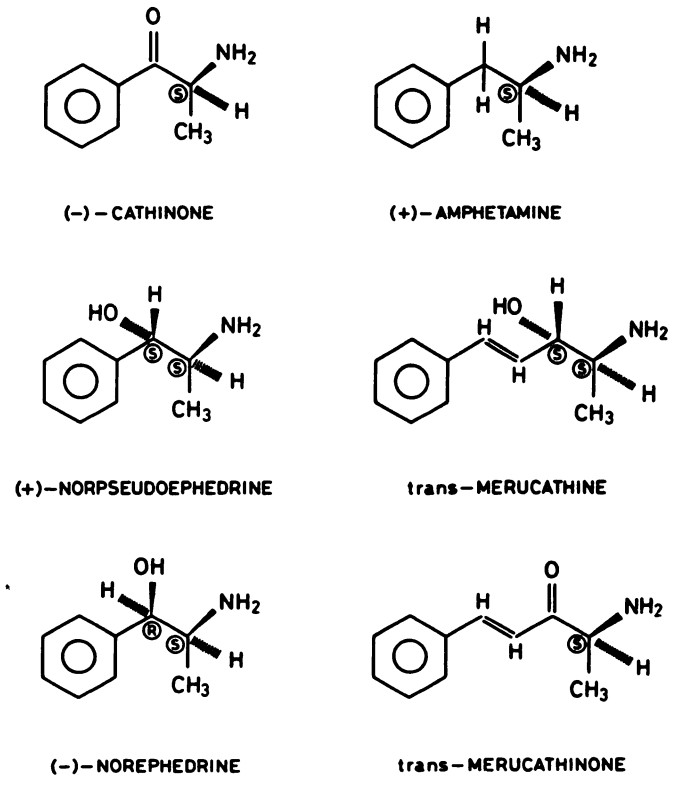
has been of scientific interest since the end of the last century when Flückiger and Gerock (32), considering also the possibility of caffeine being the active principle, analyzed the leaves. Their experiments excluded the presence of caffeine but did result in the isolation of a new alkaloid of unknown structure, for which the authors suggested the name katin. Shortly thereafter, Mosso (100) reported the isolation of an alkaline substance which he called celastrine, and which he found, in experiments on frogs, to produce effects of the sympathomimetic type. The first comprehensive study of khat constituents was made by Beitter (13), who crystallized a substance that he found to be identical with both Flückiger's katin and Mosso's celastrine. The frequently cited study of Stockman (129), who reported the isolation of several alkaloids from khat, has subsequently been questioned. The research of Wolfes reported in 1930 (142) led to the isolation of (+)norpseudoephedrine§ from khat leaves, thus identifying the compounds described by Flückiger, Mosso, and Beitter. Unfortunately, it was not stated whether fresh or dried material was used, and the latter has been presumed. Wolfe's finding led to the general belief that (+)norpseudoephedrine was the constituent responsible for the stimulating effect of khat leaves, although some years later Brücke (19) suggested that the chemistry of khat was more complex than had been assumed and that (+)norpseudoephedrine alone could not explain the effects of khat. He based his arguments on pharmacological experiments demonstrating the rather low potency of (+)norpseudoephedrine as a stimulant, and he pointed out that its concentration in the leaves would be insufficient to account for the observed effects. Years later, however, several authors (1, 61, 141) still supported the position that (+)norpseudoephedrine was the only active principle of khat. Among these, Hofmann et al. (61) based their conclusion on experiments in humans with synthetic norpseudoephedrine isomers, and Alles (1) derived his conclusions from experiments on both animals and on himself, in which the effects of fresh khat, extract of dried khat, and pure (+)norpseudoephedrine were compared. His analytical results also excluded the presence of amphetamine in khat.

These findings, as well as the demonstration of the presence of other alkaloids in khat by chromatography (112), led to a reinvestigation of the constituents of khat by modern preservation and extraction techniques (18). These techniques made possible the extraction from lyophilized leaves of substantial amounts of a compound which was found to have a stimulating effect on the locomotor activity of mice that exceeded that of synthetic (+)norpseudoephedrine and extracts from dried leaves (36). It was concluded that fresh khat contained an alkaloid that was a more potent stimulant than (+)norpseudoephedrine, but which was transformed into (+)norpseudoephedrine during the drying of the leaves.

In the investigation of the chemical composition of khat conducted by the United Nations' Narcotics Laboratory, emphasis was placed on the use of fresh material and on the appropriateness of the extraction process. The analytical studies of the Laboratory (16, 130) led to the identification of a new alkaloid, S-α-aminopropiophenone, and the name (−)cathinone was suggested for this compound (134). The spatial configuration of (−)cathinone was then studied (135), and the alkaloid was found to have the same absolute (S)configuration as (+)amphetamine (table 1); the molecule was then reproduced by synthesis (135). It was subsequently shown that (−)cathinone is present mainly in young leaves of the khat shrub (52), a finding which explains the preference of khat chewers for this type of material. A study of the alkaloid's distribution in different parts of the plant from material of various origins (124) revealed that, in some samples, (−)cathinone accounted for more than two-thirds of the total phenylalkylamines, and the market value of the leaves was found to be correlated with the (−)cathinone content. These studies also showed that (−)cathinone is a phytochemical precursor of (+)norpseudoephedrine. There is a transformation from (+)norpseudoephedrine into (−)cathinone which is rapid in adult leaves, but slow in young leaves, presumably because in the latter material, the development of the

TABLE 1

Chemical structure of the khatamines and related compounds.



§ This alkaloid is also sometimes referred to as "cathine."

enzyme apparatus is still incomplete. Similarly, the conversion of (−)cathinone into (+)norpseudoephedrine occurs when cut leaves wilt.

Although most of the (−)cathinone in khat leaves is converted into (+)norpseudoephedrine, a part of it is transformed into (−)norephedrine; the leaves contain (+)norpseudoephedrine and (−)norephedrine in a proportion of approximately 4:1 (125). The plant contains only the (−)isomer of cathinone; (+)cathinone is not present (125). A method for the stereospecific synthesis of the optical antipodes of cathinone has recently been described (97). In solution, the isomers tend to racemize, and cathinone may cyclize to dimethyldiphenylpyrazine (15). In khat of Kenyan origin, a novel phenylalkylamine has been detected, in which the ethylamine fragment of cathinone is attached to a cinnamoyl group rather than a benzoyl group (ref. 130; table 1). This finding has recently been confirmed (17), and the name merucathinone has been suggested for the compound. The corresponding hydroxyl compound, merucathine, has also been found to be present in Kenyan khat (17). The determination of the presence or absence of these two substances, along with an assessment of the ratios in which the various khat alkaloids are present in the different parts of the plant, would be of great value for a chemotaxonomic classification of the genus Catha. The total content of khatamines in commercial samples, expressed as percentage of the dry weight, varies between 0.1% (Yemen, Madagascar) and 0.5% (Kenya) (123).

Furthermore, khat leaves contain another group of alkaloids called the cathedulins, with a molecular weight ranging from 600 to 1200 (9–12). These compounds are polyesters or lactones of sesquiterpene polyols, and some features of their structure vary with the geographical origin of the plant material (24). The structure of the cathedulins is closely related to that of the previously described alkaloid cathidine D (21).

In view of these findings, the question arises as to the extent to which the different substances present in the plant contribute to the effects observed after khat chewing. Although only the phenylalkylamines (−)cathinone and (+)norpseudoephedrine have so far undergone pharmacological investigation, there is much evidence indicating that the effects observed after khat chewing can be explained by the pharmacodynamics of these two alkaloids alone. The effects of (−)cathinone and (+)norpseudoephedrine are qualitatively analogous, but (−)cathinone is considerably more potent with regard to stimulation of the central nervous system. Nevertheless, it would also be of interest to investigate the pharmacology of the other nitrogenous compounds present in khat.

Khat leaves contain small amounts of ethereal oil (114); they contain sterols and triterpenes (24), they are rich in flavonoids (39, 131), and they have a high tannin content (ref. 89: 7 to 14% in dried material). Since khat chewing causes anorexia and, consequently, inadequate food intake, the nutritional value of the material is of some interest. Although the leaves are reported to contain about 5% protein (54), their nutritional value must be considered insignificant. As to vitamins, the leaves have been reported to contain considerable amounts of ascorbic acid (101), although this could not be confirmed by the United Nations' Narcotics Laboratory in a study using fresh khat grown in Yemen (unpublished experiments).

VI. Pharmacology of The Khat Alkaloids

A. Somatic Effects

The khat alkaloid (+)norpseudoephedrine was soon recognized as being a compound with sympathomimetic properties. Thus, Brücke (19) described its effects on the blood pressure of a decapitated cat and concluded that it had an effect quantitatively and qualitatively similar to that of ephedrine. Hofmann et al. (61) confirmed these conclusions while describing the cardiovascular symptoms of the sympathetic activation induced in humans by (+)norpseudoephedrine. Furthermore, these authors showed that the alkaloid had a positive inotropic effect on the isolated frog heart, and that local application caused pronounced mydriasis in rabbits as well as in humans. They also observed that high doses of (+)norpseudoephedrine prolonged the reaction time of mice subjected to the tail flick test.

The initial studies of the pharmacology of cathinone were carried out with material synthetized by the United Nations' Narcotics Laboratory and then made available to the members of an Advisory Group of the World Health Organization; the findings of these investigators are summarized in individual reports (80, 119, 126, 144) as well as in a brief review (139). Since the new alkaloid could be expected to have sympathomimetic properties because of its chemical structure, its effects on the cardiovascular system were examined, and it was found that (−)cathinone had a positive inotropic and chronotropic effect in isolated guinea pig atria. At a bath concentration of 10 μg/ml, the effect of (−)cathinone was almost twice that of either (+)norpseudoephedrine or (+)amphetamine. In the whole animal (anaesthetized rat), however, the three compounds were equipotent in increasing the heart rate when injected i.v. at a dose of 1 mg/kg (144). Furthermore, (−)cathinone was found capable of enhancing the electrically induced constriction of isolated rabbit ear artery. In these experiments, (−)cathinone and (+)amphetamine had approximately the same effect at a concentration of 1 μg/ml, whereas the effect of (+)norpseudoephedrine was less pronounced. Additional experiments on rabbit pulmonary artery strip confirmed these results (80). The pressor effect of (−)cathinone was demonstrated in anaesthesized cats, where i.v. injection of 1 mg/kg caused a transient rise in the blood pressure by 30 to 35 mm Hg (80). A substantial rise in blood pressure, brought about by the same dose of

(−)cathinone, was also observed in anaesthesized rats. In the latter species, both (+)norpseudoephedrine and (+)amphetamine had an effect that was roughly 1.5 times that of (−)cathinone (76, 144). In these experiments, the pressor effect of the khatamines was characterized by rapid development of tachyphylaxis (80). Subsequently, the cardiovascular effects of (−)cathinone were examined in anaesthetized dogs (81) and confirmed to be analogous to those of (+)amphetamine; the two compounds were found to be equipotent. Thus, the khatamines appear to account for the effects on circulation that are associated with khat use, e.g., the exaggerated cardiovascular response to physical effort that may occur after khat chewing (38, 87).

Also in experiments on isolated cat nictitating membrane, (−)cathinone and (+)norpseudoephedrine were found to have amphetamine-like properties. In this preparation, low concentrations of amphetamine potentiate contractions induced by field stimulation, and this is also the case for the two khatamines with (−)cathinone being the more potent one. With repeated applications, tolerance to the effect of these substances can be observed, and there is cross-tolerance between the effect of the khatamines and that of amphetamine. Analogous observations were made when these substances were administered i.v. to cats, and their effect on the nictitating membrane in situ was studied (80). Similarly, (−)cathinone, like (+)amphetamine, enhances the electrically induced constriction of rat and guinea pig vas deferens (80), a finding that is relevant to the observation that habitual khat users often complain about spermatorrhea (54). Mydriasis, another sympathomimetic effect of khat use, can be related to the effect of (−)cathinone in animals. Indeed, this symptom has been consistently observed after injection of (−)cathinone to monkeys during behavioral experiments (126, 144). The flexor reflex of the hind limb of the spinal rat constitutes a useful experimental model for evaluating the action of drugs on noradrenergic neurons. In this preparation, (−)cathinone is as potent as (+)amphetamine in increasing the response, while (+)norpseudoephedrine has about one-fifth of the potency of (−)cathinone (80). These various findings indicate that the khat alkaloids (+)norpseudoephedrine and, especially, (−)cathinone have a potentiating effect on noradrenergic transmission, and that they account for the sympathomimetic effects induced by khat chewing.

An important aspect of the pharmacology of the sympathomimetic amines is their function as metabolic regulators. In this regard, it has been found that (−)cathinone increased lipolysis in vivo, an effect that could be prevented by reserpinization of the test animals (103). On the other hand, (−)cathinone antagonized norepinephrine-induced release of free fatty acids in isolated rat adipocytes (103), an effect that is similar to that of the other compounds of the amphetamine group (31). (−)Cathinone was also found to increase metabolic rate and oxygen consumption (80), which might explain the enhanced respiration caused by khat chewing (54, 87, 105), although this might also be a consequence of the hyperthermia which also occurs during khat consumption (54). The hyperthermic effect that khat produces in humans has been reproduced in rabbits by injections of (−)cathinone (67); this reponse is reminiscent of the hyperthermia usually induced by amphetamine (59). On the other hand, (−)cathinone, like (+)amphetamine, reduces the body temperature of rats previously exposed to a cold environment (P. Kalix, manuscript in preparation).

Since the amphetamines have a demonstrable analgesic effect, several studies were carried out in order to investigate whether (−)cathinone has similar properties. This was in fact found to be the case in experiments in which rats were subjected to a hot plate test. In the writhing test, however, the doses of (−)cathinone required to produce analgesia were much higher, indicating that (−)cathinone is not to be considered a true analgesic (80). Since pretreatment with an inhibitor of catecholamine synthesis was found to antagonize the induction of analgesia by (−)cathinone, it was suggested that the CNS stimulation caused by (−)cathinone plays a role in the analgesic effect (80). In further experiments in rats, using the tail flick test, cathinone was found to produce a long-lasting analgesia, the duration of which was dose related (104). Since similar findings have been reported for p-chloroamphetamine (47), the long-lasting analgesia would appear to be a property of amphetamine-like compounds in general rather than specific to (−)cathinone. In a later study (106), it was found that the acute and long-lasting analgesia induced in rats by (−)cathinone could be antagonized by catecholamine depletors as well as p-chlorophenylalanine, an inhibitor of serotonin synthesis, and it was concluded that cathinone analgesia involves activation of monoaminergic pathways mediating nociception. It was also found that high doses of the opiate antagonist naloxone interfere with cathinone analgesia. However, cathinone's effect was not modified by previous habituation of the test animals to morphine (106).

This summary of the somatic effects of the khat alkaloid (−)cathinone indicates that this substance has a pharmacological profile closely resembling that of (+)amphetamine, and that its potency is similar to that of (+)amphetamine. Since the (+)isomer of cathinone is not present in the khat plant, there has been little interest in studying its effects. It has been established, however, that (+)cathinone and (−)cathinone are of the same potency in enhancing the flexor reflex of the hind limb of the spinal rat as well as in enhancing the electrically induced constriction of the isolated rabbit ear artery (80). Similarly, the two cathinone isomers were found to be equipotent with regard to their inotropic and chron-

otropic effect on isolated guinea pig atrium (53). Racemic cathinone has been reported to be slightly less effective than the (−)isomer in increasing blood pressure and heart rate of anaesthetized rats, and to be about half as potent as (−)cathinone in eliciting a positive inotropic response in isolated guinea pig atria (144).

Little is known, at present, regarding the metabolic fate of (−)cathinone, which is likely to be different from that of (+)amphetamine because of cathinone's aminocetone structure. Preliminary studies in man (R. Brenneisen, S. Geisshüsler, and X. Schorno, manuscript in preparation) suggest that, after oral administration, (−)cathinone is metabolized rapidly into (−)norephedrine, and that it is excreted almost exclusively in this form; only about 2% of the (−)cathinone absorbed appears in unchanged form in the urine. This finding of rapid metabolism is of considerable importance in view of the possibility that the rate of inactivation of (−)cathinone is about the same as the rate of absorption of (−)cathinone during mastication of khat leaves, which would limit the cathinone blood levels attainable by chewing khat. In these experiments, it has also been found that small quantities of (−)norpseudoephedrine appear in the urine after (−)cathinone administration. Since this substance presumably is a metabolite of (+)cathinone, it can be assumed that some of the (−)cathinone undergoes racemization during the absorption process. Thus, although not present in the plant, the (+)isomer of cathinone might nevertheless contribute to a minor extent to the effects of khat. In contrast to (−)cathinone, (+)norpseudoephedrine is slowly absorbed, it has in man a serum half-life of almost 3 h (37), and it is excreted unchanged within about 24 h (92). Furthermore, it has been found that, in vitro, (+)norpseudoephedrine can be converted to (−)cathinone by dopamine-β-hydroxylase; it is possible that a conversion of this kind might occur under physiological conditions (96). It is not very likely, however, that a bioactivation of (+)norpseudoephedrine into (−)cathinone would contribute to any major extent to the effect of (+)norpseudoephedrine, an opinion supported by the finding that the two khat alkaloids have the same rapid onset of effect at the cellular level (see section VI C; ref. 72). Nevertheless, it would be of interest to investigate, in vivo, the possibility that (+)norpseudoephedrine acts, at least to a certain extent, as a prodrug for (−)cathinone.

B. Behavioral Effects

Since the characteristic property of khat is stimulation of the central nervous system, the behavioral pharmacology of khat constituents is of particular interest. Stockman (129) was the first to demonstrate in animal experiments that crystalline khat extracts could cause excitation. Much later Brücke (19), using a jiggle cage, quantified the stimulating effect of (+)norpseudoephedrine in mice. He found that the substance was approximately 100 times less potent than methamphetamine and concluded that, with regard to CNS stimulation, the khat alkaloid more closely resembled compounds of the ephedrine type rather than those of the amphetamine group. In a more recent study, Hofmann et al. (61) compared the effects of racemic norpseudoephedrine and of methamphetamine on the motor activity of mice, and they found that racemic norpseudoephedrine was only 6 times less potent than methamphetamine. They also reported that (+)norpseudoephedrine is approximately 3 times more potent than (−)norpseudoephedrine. Furthermore, they observed that, in humans, racemic norpseudoephedrine had a pronounced anorectic effect. Although doses of up to 200 mg of the substance were administered, none of the 140 subjects under study showed signs of euphoria. It was concluded that the stimulating effect of khat leaves is solely due to the presence of (+)norpseudoephedrine. In another study, in mice, of the stimulation of locomotor activity induced by (+)norpseudoephedrine, it was found that this substance had one-tenth of the potency of (+)amphetamine (30).

The availability of the new alkaloid (−)cathinone prompted several investigations of its effect or the spontaneous activity in rodents. Preliminary studies in rats (144) and mice (80) showed that s.c. administration of low doses of (−)cathinone markedly increased the locomotor activity of the animals, and that (−)cathinone had a potency approaching that of (+)amphetamine. In a study of the effects of racemic cathinone and (+)norpseudoephedrine as a function of time (148), it was found that the effect of cathinone, as well as that of (+)amphetamine, was maximal after 15 to 30 min, whereas that of (+)norpseudoephedrine, the potency of which was found to be rather low, had a much slower onset and was longer lasting. Furthermore, in a comparison of the effects of (−)cathinone and (+)amphetamine on the locomotor activity of hypophysectomized and non-operated rats (68), very similar results were obtained for the two substances. Quantitative assessments of the locomotor effect of (−)cathinone in mice indicated that the khat alkaloid had one-seventh (45) to one-fourth (137) of the potency of (+)amphetamine. In the latter study, it was also shown that cathinone's effect on locomotor activity is characterized by a dose-response curve of inverted-U shape, which is typical of stimulants of the amphetamine type. Under the conditions of these experiments, the frequency of locomotion induced by injection of a maximally effective dose of (−)cathinone was 3–5 times that of saline-injected animals. Taken together, the results of these studies show that, in rodents, (−)cathinone induces hypermotility that closely resembles that induced by (+)amphetamine, that its potency is close to that of (+)amphetamine, and that (+)norpseudoephedrine is considerably less potent than (−)cathinone.

Reserpinization has been shown to only partially antagonize the locomotor response of mice to (−)cathinone (80, 137), a finding analogous to that made earlier for

(+)amphetamine hypermotility (120). 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 appropriate for dopamine antagonism, haloperidol, spiroperidol, and pimozide blocked the locomotor response to (−)cathinone (137); this finding is in agreement with those regarding the response to (+)amphetamine (118, 133). 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.

Administration of high doses of (−)cathinone i.p. to rats was found to cause not only marked changes of the electroencephalographic (EEG) pattern, but also to induce stereotyped behavior (14). Subsequently, it was reported that, in mice, doses of (−)cathinone (11 mg/kg), injected i.p., elicited episodes of stereotyped behavior (137). Stereotyped oral activities, such as licking and gnawing, were also observed in rabbits after i.v. injection of (−)cathinone (24 mg/kg) (67). A detailed study of the stereotyped behavior induced in rats (148) revealed that the effect of racemic cathinone (20 mg/kg) was more pronounced than that of (+)amphetamine (5 mg/kg), and an effect of intermediate magnitude was obtained with (+)norpseudoephedrine (80 mg/kg). The behavior elicited by injection of apomorphine (5 mg/kg) was qualitatively different from that induced by cathinone, the effect of which was characterized mainly by repetitive head movements, but included few verticalizations. As with (+)amphetamine, pretreatment of the animals with the catecholamine synthesis blocker α-methylparatyrosine completely abolished the induction of stereotyped behavior by either (−)cathinone or (+)norpseudoephedrine. On the other hand, pretreatment with the dopamine antagonist haloperidol, which is known to specifically inhibit certain components of stereotyped behavior induced by (+)amphetamine, was found to reduce the biting and licking movements caused by cathinone. The similarity of the CNS stimulation induced by cathinone and by amphetamine was also demonstrated by a study of the effects of these two substances in rats with unilateral lesions of the substantia nigra (147). In this experimental model, direct dopamine antagonists (e.g., apomorphine) induce contralateral rotational behavior, while drugs with indirect action cause ipsilateral rotations. The latter effect was in fact observed for racemic cathinone, which was found to have, in this respect, as much as 50% of the potency of (+)amphetamine. (+)Norpseudoephedrine was also found to cause ipsilateral rotations, but the effect was longer lasting than that of cathinone, and the potency of (+)norpseudoephedrine was about one-fourth that of cathinone. In view of these findings, it was concluded that amphetamine and the khat alkaloids have the same mode of action.

Especially among the rural populations, khat leaves are often chewed in order to ease the feeling of hunger, and this anorectic effect has also been demonstrated in animal experiments by adding khat or khat extract to the food pellets of rats (90). Therapeutically, the khat alkaloid (+)norpseudoephedrine and racemic norpseudoephedrine are widely used as appetite suppressants, and the latter substance figures in the pharmacopoeia of the German Democratic Republic. In the first survey of the pharmacological properties of the new alkaloid (−)cathinone, behavioral experiments with monkeys showed an anorectic action of the compound. It has also been reported that, in rats, intracerebroventricular injection of either (−)cathinone or (+)norpseudoephedrine inhibited food intake, and this to a greater extent than (+)amphetamine (139). In another study (146), it was found that, in rats, i.p. injection of racemic cathinone resulted in reduced food intake, and that chronic administration led to a decrease in body weight. In these experiments, cathinone was found less potent than (+)amphetamine, but considerably more potent than (+)norpseudoephedrine. The effect of cathinone was characterized by the development of tolerance, which occurred almost twice as rapidly as for amphetamine. Furthermore, the development of cross-tolerance between the effects of the three compounds was observed. Cross-tolerance was also observed in a study in which the possibility of altering the sensitivity of rats to the anorectic properties of racemic cathinone by chronic amphetamine administration was investigated (34). Measurements of the consumption of sweetened milk after a period of pretreatment with the stimulants showed that, for cathinone, the development of tolerance caused a shift of the dose-response curve by a factor of 8 to 12, whereas for (+)amphetamine, the factor was only 2. The time course of the development of tolerance to the anorectic effect of racemic cathinone is illustrated by the unbroken line in fig. 1. In another study in rats (35), the effect of (−)cathinone, alone or in combination with (+)amphetamine, on the intake of a sweetened milk solution was determined. When the stimulants were given by the intragastric route, their effects were found to be additive, and that of (−)cathinone to be greater than that of (+)amphetamine. The doses required to decrease intake of the milk solution were lower for i.p. administration than for intragastric administration. It is known that, when presentation of a novel food to a rat is followed by the injection of certain psychomotor stimulants, the animal consumes less of that food on subsequent presentations (as compared to a saline-injected animal), and this aversion reaction has been termed gustatory avoidance conditioning. In such experiments, the dose of amphetamine required to establish significant aversion is about the same as that reducing food intake

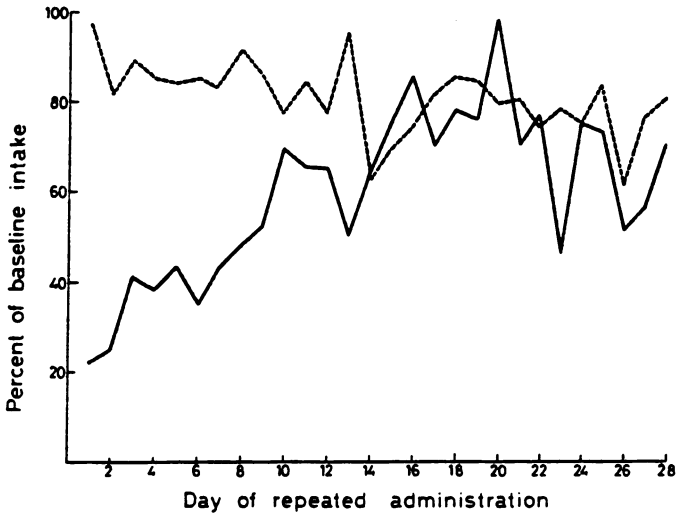


FIG. 1. The effect of repeated administrations of racemic cathinone (4 mg/kg) on the milk intake of rats as a function of the timing of the injection. Each day, the animals had access to sweetened milk during a 15-min period; they were injected either with drug 15 min before the session and with saline 15 min after the session (unbroken line), or with saline 15 min before the session and with drug 15 min after the session (broken line). Redrawn from ref. 34.

when administered before food presentation (22). In contrast, the dose of racemic cathinone required to induce gustatory avoidance responses is much higher than that which is effective when the drug is given before food presentation (33). Similarly, recent studies (48, 49) indicate that racemic cathinone is 17 times less potent than (+)amphetamine in inducing conditioned taste aversion. The surprisingly low potency of cathinone in this respect is the only obvious difference between the behavioral effects of cathinone and amphetamine that have been reported in the literature.

An important finding regarding the similarity of cathinone to amphetamine is that of Rosecrans et al. (119), who showed that racemic cathinone could be substituted for (+)amphetamine in rats trained to distinguish between a placebo and (+)amphetamine. When the substitution was made, the animals responded as if they had been given (+)amphetamine, and this response was dose related. In further studies (46, 121), rats were trained to discriminate between the stimulus properties of racemic cathinone and its vehicle in a two-lever, food-motivated operant task. Again, cathinone and (+)amphetamine produced the same response pattern, and the substances were equipotent. When the stimulus properties of (−)cathinone were compared to those of (+)cathinone and of (+)norpseudoephedrine, (−)cathinone was found to be the most potent of the three compounds (ED_{50}, 0.22 mg/kg), as compared to (+)cathinone (ED_{50}, 0.72 mg/kg) and (+)norpseudoephedrine (ED_{50}, 1.61 mg/kg) (44). In studies of the effects of cathinone and (+)amphetamine on operant behavior of primates, the two compounds were also found to be very similar, since the effects of racemic cathinone closely resembled those of (+)amphetamine with regard to modification of food-maintained behavior of rhesus monkeys (126).

Other experiments with primates illustrate the role of (−)cathinone as the dependence-producing constituent of khat leaves. Indeed, monkeys trained to press a lever for cocaine injections will continue to respond at very high rates when the training drug is replaced by (−)cathinone. In these experiments, the reinforcing effect of (−)cathinone was found to be even greater than that of (+)amphetamine (66). In another study, in which monkeys performed a drug-drug choice comparison by lever pressing, racemic cathinone was found to have a reinforcing efficacy equalling that of cocaine (143). Similar results were obtained, in monkeys, when the reinforcing efficacy of (−)cathinone was determined by using the progressive ratio paradigm (144). With this technique, it was determined that the maximal ratio values for self-administration were roughly half of those observed for cocaine. During these experiments, the monkeys made frequent injections during periods of several days, then stopping self-administration because of exhaustion, and beginning again after recovery (111). This cyclic pattern of drug intake is typical for amphetamine-dependent humans.

Taken together, the behavioral effects of (−)cathinone indicate that this alkaloid is mainly responsible for the CNS-stimulating effect of khat, and that its potency approaches that of amphetamine. (+)Norpseudoephedrine has effects similar to those of (−)cathinone, but it is less potent. Self-administration studies demonstrate that (−)cathinone enhances behavior of animals that gives them access to the substance. The high reinforcing efficacy shown by cathinone in such experiments (66, 144) combined with its surprisingly weak aversive properties (33, 48) indicates that this khat alkaloid has a high dependence potential. It can be assumed, therefore, that (−)cathinone is the dependence-producing constitutent of khat leaves.

Although it has been reported that the serotonin antagonist BC 105/B does not interfere with the discriminative stimulus effects that racemic cathinone produces in rats (119), there are some indications that cathinone has a certain specificity in affecting other aspects of serotoninergic function. It has been found, for example, that rats that had been trained in a two-lever drug-discrimination procedure were less likely to distinguish between (−)cathinone and the serotonin receptor agonist quipazine than between (+)amphetamine and quipazine (43). There is also the observation that the affinity of (−)cathinone for rat fundus serotonin receptors is 4 times higher than that of racemic amphetamine (42). On the other hand, it has been shown that chronic treatment of rats with racemic cathinone reduces the level of dopamine in several brain areas but does not affect the level of serotonin (138). It has also been found that certain parameters of the effect of (−)cathinone on conditioned

shock avoidance response can be modified by pretreatment of the animals with the serotonin receptor antagonist methysergide. Since this was also the case for (+)amphetamine, however, it can be assumed that serotoninergic systems play an inhibitory role in the effect of both stimulants (64). Finally, there is the observation that, in cats, cathinone decreases the ability to differentiate visual stimuli, and that this effect is abolished by prior administration of the serotonin synthesis blocker p-chlorophenylalanine (8). It is not clear, however, whether this observation is specific for cathinone or whether it also applies to the other stimulants of the amphetamine group. Thus, the relevance of serotonin pathways in the behavioral effects of cathinone should be studied in greater depth.

Since the CNS-stimulating effect of khat may reach the level of acute toxicity upon consumption of very large amounts or exceptionally potent material (4, 23, 26, 41, 50, 58), the CNS toxicity of the constituents of khat has been assessed. In mice, the LD_{50} of (+)norpseudoephedrine was determined as 275 mg/kg (61), or 160 mg/kg (30), and (+)norpseudoephedrine was estimated to be about 13 times less toxic than (+)amphetamine (30). The lethality of racemic cathinone has been found to be approximately one-third that of (+)amphetamine in a test in which the substances were administered to mice in repeated doses over a 24-h period (63); in these experiments, the toxicity of cathinone was increased by pretreatment with methylsergide at doses that did not modify the LD_{50} of (+)amphetamine. The chronic toxicity of the khat alkaloids has been evaluated in neurochemical studies which indicate that, in rats, long-term administration of cathinone results in a significant depletion of dopamine from the caudate, telencephalon, and midbrain (138), and this has also been observed after repeated administration of high doses of (+)norpseudoephedrine (C. Schuster, personal communication).

C. Cellular Effects

Since the somatic and behavioral effects of (−)cathinone were found to closely resemble those of (+)amphetamine, a number of studies addressed the question of whether (−)cathinone might not also have amphetamine-like effects at the cellular and subcellular levels. The first of these was a neurochemical investigation of the properties of (−)cathinone by Rosecrans et al. (119), who found that cathinone modified brain catecholamine turnover, although to a lesser extent than (+)amphetamine. In mice pretreated with (−)cathinone (8 mg/kg), for example, the tunnover of dopamine was found to be increased by 32%, but that of norepinephrine was practically unaffected. It is of interest to note that, in rats, repeated administration of racemic cathinone produced, in several brain regions, a long-lasting depletion of dopamine but had no effect on the level of norepinephrine (138). In studies of the effect of cathinone on dopamine uptake in slices of rat striatum, the concentration required for half-maximal inhibition was found to be 3 μM. In this respect, racemic amphetamine was 5 times more potent, while (+)norpseudoephedrine was about 8 times less potent than cathinone (147). In analogous experiments on synaptosomes prepared from rat neostriatum, half-maximal inhibition of dopamine uptake was obtained at a concentration of 2.5 μM racemic cathinone (138). Since amphetamine is known to have an inhibitory effect on monoaminooxidase, studies were made to determine whether this was also the case for (−)cathinone and (+)norpseudoephedrine. Using an assay system involving beef plasma monoaminooxidase and benzylamine as a substrate, it was found that (−)cathinone was considerably more potent in this respect than racemic amphetamine, whereas (+)norpseudoephedrine had approximately the same potency as racemic amphetamine (107). These results obtained in vitro are consonant with the observation that, in subjects not accustomed to khat chewing, the urinary output of catecholamines (although not that of 3-methoxy-4-hydroxymandelic acid) tends to increase after consumption of the drug (107).

It has been demonstrated that unimpaired functioning of dopaminergic neurotransmission is required for maintaining amphetamine self-administration (117). The finding, that the amphetamine analog cathinone can inhibit dopamine uptake, might suggest that its effects are produced by a blocking of the reuptake of physiologically released dopamine, i.e., by prolonging the action of dopamine on its receptors. Another possibility would be that cathinone acts by inducing the release of dopamine from presynaptic storage sites, a mechanism considered mainly responsible for the action of amphetamine on dopaminergic transmission (51). Therefore, the effect of (−)cathinone on the efflux of radioactivity from isolated rabbit caudate nucleus prelabeled with ^{3}H-dopamine was studied (69). It was found that superfusion of the tissue with 4 μM (−)cathinone resulted in a rapid and reversible increase of the efflux of radioactivity. Superfusion with the same concentration of (+)amphetamine caused an increase in efflux of an amplitude comparable to that produced by (−)cathinone, whereas (+)norpseudoephedrine, at the same concentration, had no effect. Similar findings were reported subsequently by Zelger and Carlini (147), who showed that, in ^{3}H-dopamine-prelabeled rat striatal slices, racemic cathinone, at a concentration of 5 μM, had about two-thirds of the effectiveness of (+)amphetamine in inducing the release of radioactivity, and that, at 50 μM, the two compounds were almost equipotent. The releasing effect of racemic cathinone was also demonstrated in ^{3}H-dopamine-preloaded synaptosomes obtained from rat neostriatum. In these experiments, the dose-response curve for cathinone was found to be less steep than that for (+)amphetamine (138). The repeated demonstration that cathinone has, in vitro, a releasing effect at dopaminergic synapses is consonant with the in vivo finding that chronic high-

dose treatment of rats with cathinone results in a depletion of dopamine from the caudate, telencephalon, and midbrain (138). It has also been reported that (−)cathinone, although approximately 5 times less potent, decreases the levels of the dopamine metabolite 3,4-dihydroxyphenylacetic acid, in several areas of rat brain, in the same manner as (+)amphetamine (98); this would reflect a decrease in the availability of dopamine for intraneuronal metabolism. The concept that the effect of (−)cathinone on dopaminergic transmission is similar to that of (+)amphetamine is further supported by electrophysiological data showing that, in rats, injection of (−)cathinone is followed by a reduction of the firing rate of certain neurons in the substantia nigra (98), an effect characteristic of (+)amphetamine. (−)Cathinone is about equipotent to (+)amphetamine in producing this effect, which has been explained by induction of dopamine release in the striatum leading to striato-nigral inhibition (20).

The dopaminergic structures of the nucleus accumbens are essential for the induction of locomotor activity by amphetamine (77). Since (−)cathinone causes hypermotility of the amphetamine type, its effect on the release of radioactivity from ^{3}H-dopamine-prelabeled rat nucleus accumbens tissue was investigated. It was found that a substantial release of radioactivity could be induced by (−)cathinone as well as by (+)amphetamine, at a concentration of 3 μM (fig. 2). In the same tissue, the potency of (−)cathinone with regard to release induction was compared to that of (+)norpseudoephedrine, and it was found that 8 times the concentration of (+)norpseudoephedrine was required to reproduce the effect of a given dose of (−)cathinone (72). A similar potency ratio for the two alkaloids had been observed previously in release experiments with rat striatum (147). In other experiments, the releasing effect of (−)cathinone was found to be pharmacologically analogous to that of (+)amphetamine. In order to determine whether the (−)cathinone-induced efflux of radioactivity was due to an enhanced release from intracellular sites, or due to an inhibition of reuptake of spontaneously released material, the effect of (−)cathinone was examined in rabbit

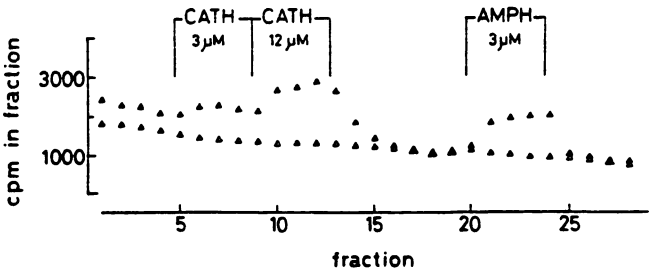


FIG. 2. The effect of (−)cathinone (CATH) and (+)amphetamine (AMPH) on the release of radioactivity from rat nucleus accumbens tissue prelabeled with ^{3}H-dopamine. The efflux from an unstimulated control preparation superfused simultaneously with saline is indicated by open triangles. Each fraction corresponds to 3 min of efflux. From ref. 71.

caudate nucleus slices preperfused with one of the catecholamine reuptake inhibitors cocaine, benztropine, nomifensine, or mazindol (70, 71). At the concentrations tested, these substances had very little or no effect on the resting efflux of radioactivity from the preparation, but they antagonized the stimulation of efflux induced by (−)cathinone. It can thus be concluded that release induction is the mechanism underlying cathinone's effect with inhibition of transmitter uptake playing only a minor role. Since analogous conclusions have been reached with regard to (+)amphetamine (56, 57), it can be assumed that the two stimulants have the same mechanism of action (74).

Amphetamine is also known to affect serotoninergic pathways in the CNS (128) and has been found, in rat corpus striatum, to release serotonin in a dose-dependent manner (5). In order to determine whether (−)cathinone can mimic this aspect of amphetamine action, its effect on the release of radioactivity from rat striatal tissue prelabeled with ^{3}H-serotonin was studied. It was found that, in order to produce an effect of an amplitude similar to that produced by a given concentration of (+)amphetamine, a 3 times higher concentration of (−)cathinone was needed (75). This indicates that, with regard to release from serotonin storage sites, (−)cathinone has no greater specificity than (+)amphetamine. There are indications, however, that interaction with serotonin pathways might contribute to the CNS effects of (−)cathinone (8), and there is also the interesting observation that, in the rat fundus preparation, the affinity of (−)cathinone for serotonin receptors is 4 times greater than that of (+)amphetamine (42).

Since the consumption of khat causes a number of symptoms of the sympathomimetic type, especially at the cardiovascular level, an investigation was made to determine whether these were due to release of norepinephrine from sympathetic nerve endings. Experiments analogous to those on CNS tissue described above were carried out with slices of rabbit heart tissue that had been prelabeled with ^{3}H-norepinephrine. It was found that, in this tissue as well, superfusion with (−)cathinone caused a substantial increase of the release of radioactivity, and that the potency of (−)cathinone, like that of (+)amphetamine, was almost one order of magnitude greater than in CNS tissue (73). Furthermore, the effect of (−)cathinone could be modified by the same pharmacological manipulations as that of (+)amphetamine; for example, reserpinization of the animals was found to result in rapid development of tachyphylaxis. The releasing effect of (−)cathinone could also be blocked by preperfusing the tissue with desipramine or cocaine; the efflux inhibition caused by cocaine was shown to be unreleated to its local anaesthetic properties (73). Taken together, these experiments demonstrate that (−)cathinone has a releasing effect on peripheral norepinephrine storage sites, and they support the conclusion (80) that

(−)cathinone facilitates noradrenergic transmission. It was also found, however, that, in ^{3}H-norepinephrine-prelabeled rabbit atrium slices, (+)norpseudoephedrine and (−)cathinone are equipotent with regard to inducing release (72), and this finding is consonant with the observation that, in anaesthetized rats, (+)norpseudoephedrine and (−)cathinone have about the same potency in increasing heart rate and blood pressure (76, 144). Thus, with regard to their peripheral effects, the two khat alkaloids appear to play an equal role.

The findings that, although (−)cathinone and its synthetic enantiomer (+)cathinone are about equipotent in inducing sympathomimetic effects in isolated organs (53, 80), (−)cathinone is roughly 5 times more potent than (+)cathinone in stimulating the locomotor activity of mice (45) and rats (53) and also more potent with regard to discriminative stimulus properties in rats (44), suggested the need to study these differences at the cellular level. An attempt was made, therefore, to compare the two cathinone isomers with regard to their releasing effect on catecholamine storage sites of the peripheral and central nervous system of the rat. It was found, in fact, that (−) and (+)cathinone had about the same potency in increasing the efflux of radioactivity from vas deferens or atrial tissue prelabeled with ^{3}H-norepinephrine, but that (−)cathinone was approximately 3 times more potent than (+)cathinone in inducing release from ^{3}H-dopamine-prelabeled nucleus accumbens or striatal tissue (P. Kalix, manuscript submitted).

VII. Conclusions and Perspectives

The effects desired by khat chewers are those associated with stimulation of the central nervous system and, sometimes, that of anorexia. Pharmacological experiments have shown a correlation between the symptoms of stimulation observed after khat consumption and those seen in animals after administration of the khat alkaloid (−)cathinone. Similarly, it is now possible to explain the compulsiveness of khat intake observed in some of the chewers by the reinforcing properties of (−)cathinone, which have been demonstrated in self-administration experiments with monkeys. Furthermore, (−)cathinone can be considered a potent amphetamine-like compound, since in almost all respects its effects are analogous to those of (+)amphetamine; indeed, no major pharmacological difference between the khat alkaloid and the synthetic stimulant has been discerned. The key observation demonstrating this is the finding that (−)cathinone and (+)amphetamine have the same mechanism of action; both substances induce release from CNS dopamine terminals and thus increase the activity of dopaminergic pathways. These results confirm the assumption that khat is an amphetamine-like material (27) and show that the chewing of a portion of khat is pharmacologically equivalent to the intake of a certain dose of amphetamine. The pronounced quantitative differences between the CNS effects of (−)cathinone and (+)norpseudoephedrine suggest that the latter alkaloid plays only a subsidiary role in the stimulatory action of khat.

The somatic effects observed after khat consumption are characterized by a sympathomimetic syndrome. Again, the symptoms of this reaction can be reproduced by administering (−)cathinone to animals and by experiments on isolated tissue, and here also the observed effects are analogous to those of (+)amphetamine. In vitro experiments indicate that these effects are due to an induction of release at peripheral norepinephrine storage sites leading to increased transmission of sympathetic signals. With regard to their capacity to induce release from these sites, (−)cathinone and (+)norpseudoephedrine have approximately the same potency, and the two compounds are also equipotent in inducing certain sympathomimetic effects in whole animals. Thus, if present at the same concentration, the two khat alkaloids would contribute to about the same extent to the sympathomimetic effects of khat.

Since khat leaves usually contain more (+)norpseudoephedrine than (−)cathinone (124), the peripheral effects induced by a portion of khat can be considered to be predominantly due to (+)norpseudoephedrine. In cases where the content of (+)norpseudoephedrine is particulary high, this alkaloid can also be expected to contribute significantly to the CNS effects of khat. Thus, the greater the contribution of (+)norpseudoephedrine to the CNS effects, the more pronounced the sympathomimetic side effects of a given batch of khat will be. The khat chewer, therefore, will prefer leaves that contain a high proportion of (−)cathinone, not only because these are a better stimulant, but also because they are less prone to produce the undesired peripheral effects. Consideration must also be given to the pharmacokinetics of the two compounds, since (−)cathinone can be presumed, because of its greater lipophilicity, to penetrate more easily into the CNS than (+)norpseudoephedrine. Blood level measurements of the two compounds would be desirable not only for animal experiments with khat constituents, but also for investigating the absorption and distribution of the alkaloids during khat chewing. To date, there has only been a study of the bioavailability of (+)norpseudoephedrine from capsules (37), while a high-pressure liquid chromatography (HPLC) assay for cathinone is being developed (62).

Although the effects of khat chewing can be satisfactorily explained by the presence of (−)cathinone and (+)norpseudoephedrine in the leaves, it cannot be excluded that other khat constituents might be involved in the khat syndrome. It is also possible that (−)cathinone has other pharmacological properties that have not yet been recognized. In view of the usually chronic use of khat, it seems also necessary to give more attention to the possibility of long-term adverse effects, e.g., to the carcinogenic and teratogenic potential of the drug.

Acute and immediate medical problems arising from khat consumption are infrequent, probably because the alkaloids are "diluted" in the bulk material of the leaves. The main concern with regard to khat chewing is the wide range of indirect health, social, and economic consequences of the habit. It must be granted, however, that the khat habit has certain positive aspects, since it furthers social interaction and structures social life. This is the predominant reason for its long tradition and wide social acceptance, especially in Yemen where the khat session is, for most males, the main recreational activity. Considering the problem in this perspective, the limits between use and abuse of khat become difficult to discern. It must also be recalled that some khat chewers have non-recreational motives since, particularly among the rural populations, the drug is also used for improving work performance and to lessen the feeling of hunger.

Khat use has been endemic in East Africa and the Arabian peninsula for many centuries. During the last decades, however, its use has spread considerably, probably because of more efficient transportation of this perishable commodity as well as because of the disappearance of social constraints that formerly determined the pattern of habitual khat use. The serious socioeconomic repercussions of these developments, as well as the resulting increase in health problems, have stimulated efforts to restrain the cultivation and use of the drug. It has been found, however, that prohibition of khat is difficult to enforce and has little effect. More gradual approaches such as reducing the availability of khat by restricting the marketing of the leaves may have better chances of success. This has already been tried in North Yemen, where khat markets have been moved to the outskirts of the population centers, and in South Yemen, where khat is sold only on holidays. Of course, such regulatory measures should be supported by crop substitution programs for those who derive their income from khat, and by creating alternative recreational activities.

The question may arise as to whether khat use will evolve in the same way as the habit of chewing coca leaves, i.e., from the local use of a natural stimulant to the abuse of its main active principle in regions far from the areas of cultivation of the plant. This is unlikely because (−)cathinone is difficult to extract from the leaves and, on the other hand, it is more difficult to synthesize than its pharmacological analog amphetamine.

The epidemic spreading of khat use in some developing countries demonstrates the vulnerability of these populations to drug-related problems. However, the countries concerned are now beginning to cooperate in dealing with these problems in much the same manner as was done for opium at the beginning of the century. Thus, two international conferences devoted to the problems associated with khat use have recently been held in East Africa, resulting in resolutions which not only reflect the complexities of the issue, but also the deep concern that it causes.

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REFERENCES

1. Alles, G., Fairchild, D., and Jensen, M.: Chemical pharmacology of Catha edulis. J. Med. Pharm. Chem. **3:** 323–352, 1961.
2. Al-Meshal, I.: Characterization and evaluation of Saudi Arabian khat. *In* Abstracts, First International Conference on Khat, ed. by International Council on Alcohol and Addictions, pp. 110–135, Lausanne, Switzerland, 1983.
3. Al-Meshal, I., Ageel, A., Tariq, M., and Parmar, N.: The gastric anti-ulcer activity of khat (Catha edulis). Res. Commun. Subst. Abuse **4:** 143–150, 1983.
4. Ardouin, C., and Gendron, Y.: Manifestations psychiatriques de l'intoxication au khat. Méd. Armées **4:** 407–410, 1976.

4a. Azayem, A.: Nature and extent of the socio-medical aspects of drug dependence in the Yemen Arab Republic. Unpublished WHO Document EM/MENT/56, 1973.

5. Azzaro, A., and Rutledge, C.: Selectivity of release of norepinephrine, dopamine, and 5-hydroxytryptamine by amphetamine in various regions of rat brain. Biochem. Pharmacol. **22:** 2801–2813, 1973.
6. Baasher, T.: The use of khat: a stimulant with regional distribution. WHO Public Health Pap. **73:** 86–93, 1980.
7. Baasher, T., and Sadoun, R.: The epidemiology of khat chewing in the Republic of Djibouti. Unpublished WHO Document EM/MENT/102, 1983.
8. Babayan, E., Bharkov, N., and Machula, A.: Mediator mechanisms of cathinone effects on animal behaviour. Drug Alcohol Depend. **12:** 31–35, 1983.
9. Baxter, R., Crombie, L., Simmonds, D., and Whiting, D.: Extractives of Catha edulis: occurrence of celastraceous alkaloids having mono- and bis-macrolide bridges. J. Chem. Soc. Chem. Commun. **1976:** 463–465, 1976a.
10. Baxter, R., Crombie, L., Simmonds, D., and Whiting, D.: Structures of cathedulin-2 and cathedulin-8, new sesquiterpene alkaloids from Catha edulis. J. Chem. Soc. Chem. Commun. **1976:** 465–466, 1976b.
11. Baxter, R., Crombie, L., Simmonds, D., Whiting, D., Braenden, O., and Szendrei, K.: Alkaloids of Catha edulis (khat). Isolation and characterisation of eleven new alkaloids with sesquiterpene cores (Cathedulins). J. Chem. Soc. Chem. Commun. **1979:** 2965–2971, 1979.
12. Baxter, R., Crombie, M., Crombie, L., Simmonds, D., Whiting, D., and Szendrei, K.: Alkaloids of Catha edulis (khat). Structures of cathedulins E3, E4, E5, E6, and K12. Novel sesquiterpene alkaloids with mono- and bismacrolide bridges. J.Chem. Soc. Chem. Commun. **1979:** 2982–2989, 1979.
13. Beitter, A.: Pharmakognostisch-chemische Untersuchung von Catha edulis. Arch. Pharm. (Weinheim) **239:** 17–33, 1901.
14. Berardelli, A., Capocaccia, L., Pacitti, C., Tancredi, V., Quinteri, F., and Elmi, A.: Behavioural and EEG effects induced by an amphetamine-like substance (cathinone) in rats. Pharmacol. Res. Commun. **12:** 959–964, 1980.
15. Berrang, B., Lewin, A., and Carroll, F.: Enantiomeric aminopropiohenones: preparation and investigation. J. Org. Chem. **47:** 2643–2647, 1982.
16. Braenden, O.: Research on the chemical composition of khat. *In* Problems of Drug Dependence, NIDA Research Monograph **27:** pp. 320–321, U.S. Government Printing Office, Washington, DC, 1979.
17. Brenneisen, R., Geisshüsler, S., and Schorno, H.: Merucathin, ein neues Phenylalkylamin aus Khat (Catha edulis). Planta Med. **50:** 531, 1984.
18. Brilla, R.: Uber den zentralerregenden Wirkstoff der frischen Blätter von Catha edulis Forskal. Thesis, University of Bonn/GFR, 1962.
19. Brücke, F.: Uber die zentralerregende Wirkung des Alkaloides Cathin. Arch. Exp. Pathol. Pharmakol. **198:** 100–106, 1941.
20. Bunney, B., and Aghajanian, G.: Amphetamine-induced inhibition of central dopaminergic neurons: mediation by a striato-nigral feedback pathway. Science (Wash. DC) **192:** 391–393, 1976.
21. Cais, M., Ginsburg, D., Mandelbaum, A., and Smith, R.: Constituents of Catha edulis: isolation and structure of cathidine D. Tetrahedron **31:** 2727–2731, 1975.
22. Carey, R.: A comparison of the food suppression produced by giving amphetamine as an aversion treatment versus as an anorexic treatment. Psychopharmacology **56:** 45–48, 1978.
23. Carothers, J.: Miraa as a cause of insanity. East Afr. Med. J. **22:** 4–6, 1945.
24. Crombie, L.: The cathedulin alkaloids. Bull. Narc. **32:** 37–50, 1980.
25. DeHondt, H., Fahmy, A., and Abdelbaset, S.: Chromosomal and biochemical studies on the effect of kat extract on laboratory rats. Environ. Mutagen. **6:** 851–860, 1984.

26. DHADPHALE, M., MENGECH, A., AND CHEGE, S.: Miraa (Catha edulis) as a cause of psychosis. East Afr. Med. J. **58:** 130–135, 1981.
27. EDDY, N., HALBACH, H., ISBELL, H., AND SEEVERS, M.: Drug dependence: its significance and characteristics. Bull. WHO **32:** 721–733, 1965.
28. ELMI, A.: The chewing of khat in Somalia. J. Ethnopharmacol. **8:** 163–176, 1983a.
29. ELMI, A.: Khat and blood glucose levels in man. J. Ethnopharmacol. **8:** 331–334, 1983b.
30. FAIRCHILD, M., AND ALLES, G.: The central locomotor stimulatory activity and acute toxicity of the ephedrine and norephedrine isomers in mice. J. Pharmacol. Exp. Ther. **158:** 135–139, 1967.
31. FINGER, D., AND FELLER, K.: Lipolytic action of structurally related agonists in rat epidydimal fat tissue. Biochem. Pharmacol. **19:** 705–713, 1970.
32. FLÜCKIGER, F., AND GEROCK, J.: Contributions to the knowledge of Catha leaves. Pharmacol. J. Trans. **18:** 221–224, 1887.
33. FOLTIN, R., AND SCHUSTER, C.: The effects of DL-cathinone in a gustatory avoidance paradigm. Pharmacol. Biochem. Behav. **14:** 907–909, 1981.
34. FOLTIN, R., AND SCHUSTER, C.: Behavioural tolerance and cross-tolerance to DL-cathinone and D-amphetamine in rats. J. Pharmacol. Exp. Ther. **222:** 126–131, 1982.
35. FOLTIN, R., WOOLVERTON, W., AND SCHUSTER, C.: Effects of psychomotor stimulants, alone and in pairs, on milk drinking in the rat after intraperitoneal and intragastric administration. J. Pharmacol. Exp. Ther. **226:** 411–418, 1983.
36. FRIEBEL, H., AND BRILLA, R.: Uber den Wirkstoff der frischen Blätter und Zweigspitzen von Catha edulis. Naturwissenschaften **50:** 354–355, 1963.
37. FROSCH, F.: Biopharmazeutische Untersuchungen an D-Norpseudoephedrin. Arzneim.-Forsch. **27:** 665–668, 1977.
38. GALKIN, V., AND MIRONYCHEV, A.: Effect of the narcotic kat (Catha edulis) on certain functions of the human body. Fed. Proc. **23:** T741–742, 1964.
39. GELLERT, M., SZENDREI, K., AND REISCH, J.: Dihydromyricetin-3-0-rhamnoside from leaves of Catha edulis. Phytochemistry **20:** 1759–1760, 1981.
40. GENDRON, Y., ARDOUIN, C., AND MARTINE, J.: Accidents cardio-vasculaires aigus déclenchés par le khat. Méd. Trop. **37:** 69–73, 1977.
41. GIANNINI, A., AND CASTELLANI, S.: A manic-like psychosis due to khat (Catha edulis). J. Toxicol. Clin. Toxicol. **19:** 455–459, 1982.
42. GLENNON, R., AND LIEBOWITZ, S.: Serotonin receptor affinity of cathinone and related analogues. J. Med. Chem. **25:** 393–397, 1982.
43. GLENNON, R., AND ROSECRANS, J.: Speculations on the mechanism of action of hallucinogenic indolealkylamines. Neurosci. Biobehav. Rev. **5:** 197–207, 1981.
44. GLENNON, R., SCHECHTER, M., AND ROSECRANS, J.: Discriminative stimulus properties of S(−)- and R(+)-cathinone. (+)cathine, and several structural modifications. Pharmacol. Biochem. Behav. **21:** 1–4, 1984.
45. GLENNON, R., AND SHOWALTER, D.: The effect of cathinone and several related derivatives on locomotor activity. Res. Commun. Subst. Abuse **2:** 186–192, 1981.
46. GLENNON, R., YOUNG, R., HAUCK, A., AND MCKENNEY, J.: Structure-activity studies on amphetamine analogs using drug discrimination methodology. Pharmacol. Biochem. Behav. **21:** 895–901, 1984.
47. GÖRLITZ, B., AND FREY, H.: Central monoamines and antinociceptive drug action. Eur. J. Pharmacol. **20:** 171–180, 1972.
48. GOUDIE, A.: Comparative effects of cathinone and amphetamine on fixed interval operant responding: a rate-dependency analysis. Pharmacol. Biochem. Behav., in press, 1985.
49. GOUDIE, A., ATKINSON, J., NEWTON, T., AND DEMELLWEEK, C.: Discriminative and aversive actions of *dl*-cathinone and *d*-amphetamine in rats: comparison with effects on operant responding and water intake. Psychopharmacology **82:** S3, 1984.
50. GOUGH, S., AND COOKSON, I.: Khat-induced schizophreniform psychosis in UK. Lancet **8374:** 455, 1984.
50a. GREENWAY, P.: Khat. East Afr. Agr. J. **13:** 98–102, 1947.
51. GROVES, P., AND REBEC, G.: Biochemistry and behaviour: some central actions of amphetamine and antipsychotic drugs. Annu. Rev. Psychol. **27:** 91–127, 1976.
52. GUANTAI, A., AND MAITAI, C.: Relative distribution of cathinone and norpseudoephedrine in Catha edulis growing in Kenya. East Afr. Med. J. **59:** 394–398, 1982.
53. GUGELMANN, R., VON ALLMEN, M., BRENNEISEN, R., AND PORZIG, H.: Quantitative differences in the pharmacological effects of (+) and (−)cathinone. Experientia (Basel), in press, 1985.
54. HALBACH, H.: Medical aspects of the chewing of khat leaves. Bull. WHO **47:** 21–29, 1972.
55. HEACOCK, R., AND FORREST, J.: Khat. Can. J. Pharm. Sci. **9:** 64–66, 1974.
56. HEIKKILA, R., ORLANSKY, H., AND COHEN, G.: Studies on the distinction between uptake inhibition and release of ^{3}H-dopamine in rat brain tissue slices. Biochem. Pharmacol. **24:** 847–852, 1975.
57. HEIKKILA, R., ORLANSKY, H., MYTILINEOU, C., AND COHEN, G.: Amphetamine: evaluation of *d*- and *l*-isomers as releasing agents and uptake inhibitors for ^{3}H-dopamine and ^{3}H-norepinephrine in slices of rat neostriatum and cerebral cortex. J. Pharmacol. Exp. Ther. **194:** 47–56, 1975.
58. HEISCH, R.: A case of poisoning by Catha edulis. East Afr. Med. J. **22:** 7–9, 1945.
59. HILL, H., AND HORITA, A.: Inhibition of amphetamine hyperthermia by blockade of dopamine receptors in rabbits. J. Pharm. Pharmacol. **23:** 715–717, 1971.
60. HODGKINSON, R.: A study of the clinical effects of Catha edulis in Kenya. Med. J. Aust. **49:** 884–886, 1962.
61. HOFMANN, H., OPITZ, K., AND SCHNELLE,H.: Die Wirkung des Norpseudoephedrins. Arzneim.-Forsch. **5:** 367–370, 1955.
62. HORSTMANN, M., OPITZ, K., AND ABDI, S.: Blood levels and duration of action of (+)cathinone in the rat. Naunyn-Schmiedebergs Arch. Exp. Pathol. Pharmakol. **325:** R24, 1984.
63. HUANG, D., AND WILSON, M.: The role of dopaminergic and serotoninergic systems in the acute lethal effects of *dl*-cathinone, *d*-amphetamine, and cocaine in mice: a comparative study. Res. Commun. Subst. Abuse **4:** 215–225, 1983.
64. HUANG, D., AND WILSON, M.: The effects of *dl*-cathinone, *d*-amphetamine, and cocaine on avoidance responding in rats and their interactions with haloperidol and methysergide. Pharmacol. Biochem. Behav. **20:** 721–729, 1984.
65. HUGHES, P.: Khat chewing in Yemen. *In* Papers presented at the Fourth International Institute on the Prevention and Treatment of Drug Dependence, ed. by the International Council on Alcoholism and Addictions, pp. 32–46, Lausanne, Switzerland, 1973.
66. JOHANSON, C., AND SCHUSTER, C.: A comparison of the behavioural effects of L- and DL-cathinone and D-amphetamine. J. Pharmacol. Exp. Ther. **219:** 355–362, 1981.
67. KALIX, P.: Hyperthermic response to (−)cathinone, an alkaloid of Catha edulis (Khat). J. Pharm. Pharmacol. **32:** 662–663, 1980a.
68. KALIX, P.: Hypermotility of the amphetamine-type induced by a constituent of khat leaves. Br. J. Pharmacol. **68:** 11–13, 1980b.
69. KALIX, P.: A constituent of khat leaves with amphetamine-like releasing properties. Eur. J. Pharmacol. **68:** 213–215, 1980c.
70. KALIX, P.: Cathinone, an alkaloid from khat leaves with an amphetamine-like releasing effect. Psychopharmacology **74:** 269–270, 1981.
71. KALIX, P.: The amphetamine-like releasing effect of the alkaloid (−)cathinone on rat nucleus accumbens and rabbit caudate nucleus. Prog. Neuropsychopharmacol. Biol. Psychiatr. **6:** 43–49, 1982.
72. KALIX, P.: A comparison of the catecholamine releasing effect of the khat alkaloids (−)cathinone and (+)norpseudoephedrine. Drug Alcohol Depend. **11:** 395–401, 1983a.
73. KALIX, P.: Effect of the alkaloid (−)cathinone on the release of radioactivity from rabbit atria prelabelled with ^{3}H-norepinephrine. Life Sci. **32:** 801–807, 1983b.
74. KALIX, P.: Mechanism of action of (−)cathinone, a new alkaloid from khat leaves. Alcohol. Alcoholism **18:** 301–303, 1983c.
75. KALIX, P.: Effect of the alkaloid (−)cathinone on the release of radioactivity from rat striatal tissue prelabelled with ^{3}H-serotonin. Neuropsychobiology **12:** 127–129, 1984.
76. KAWAGUCHI, T., IIZUKA, H., AND YANAGITA, T.: Pharmacological effects of active ingredients of khat. Jpn. J. Pharmacol. **29;** 72P, 1979.
77. KELLY, P., AND IVERSEN, S.: Selective 6-OH-DA-induced destruction of mesolimbic dopamine neurons: abolition of psychostimulant-induced locomotor activity in rats. Eur. J. Pharmacol. **40:** 45–56, 1976.
78. KENNEDY, J., TEAGUE, J., AND FAIRBANKS, L.: Qat use in North Yemen and the problem of addiction. A study in medical anthropology. Cult. Med. Psychiatry **4:** 311–344, 1980.
79. KENNEDY, J., TEAGUE, J., ROKAW, W., AND CONNEY, E.: A medical evaluation of the use of qat in North Yemen. Soc.Sci. Med. **17:** 783–793, 1983.
80. KNOLL, J.: Studies on the effects of (−)cathinone. *In* Problems of Drug Dependence. NIDA Research Monograph **27:** pp. 322–323, U.S. Government Printing Office, Washington, DC, 1979.
81. KOHLI, J., AND GOLDBERG, L.: Cardiovascular effects of (−)cathinone in the anaesthetized dog: comparison with (+)amphetamine. J. Pharm. Pharmacol. **34:** 338–340, 1982.
82. KRIKORIAN, A.: Khat and its use: a historical perspective. J. Ethnopharmacol. **12:** 115–178, 1984.
83. KRIKORIAN, A., AND GETAHUN, A.: Chat: coffee's rival from Harar, Ethiopia. I. Botany, cultivation and use. Econ. Bot. **27:** 353–377, 1973.
84. LAURENT, J.: Toxique et toxicomanie peu connus, le cath. Ann. Méd. Psychiatrie **120;** 649–657, 1962a.
85. LAURENT, J.: Conséquences médicales de la toxicomanie au cath. Méd. Trop. **22:** 477–483, 1962b.
86. LEAGUE OF NATIONS: Document O.C. 1617 (3 Feb. 1936).
87. LEBRAS, M., AND FRETILLERE, Y.: Les aspects médicaux de la consommation habituelle du cath. Méd. Trop. **25:** 720–732, 1965.
88. LEMORDANT, D.: Toxicité et antagonistes du khat. Méd. Trop. **26:** 124–129, 1966.
89. LUQMAN, W., AND DANOWSKI, T.: The use of khat in Yemen: social and medical observations. Ann. Intern. Med. **85:** 246–249, 1976.
90. MAITAI, C.: The toxicity of the plant Catha edulis in rats. Toxicon **15:** 363–366, 1977.
91. MAITAI, C.: Country report on khat in Kenya. *In* Abstracts, First International Conference on Khat, ed. by International Council on Alcohol and Addictions, pp. 87–90, Lausanne, Switzerland, 1983.
92. MAITAI, C., AND MUGERA, G.: Excretion of the active principle of Catha edulis (Miraa) in human urine. J. Pharm. Sci. **64:** 702–703, 1975.

93. MANCIOLI, M., AND PARINELLO, A.: Il qat (Catha edulis). La Clin. Terapeutica (Roma) **43:** 103–172, 1967.
94. MARESOVA, Z.: Kat, a little known stimulant. Vnitrni Lekarstvi **13:** 753–759, 1967.
95. MARGETTS, E.: Miraa and myrrh in East Africa—clinical notes about Catha edulis. Econ. Bot. **21:** 358–362, 1967.
96. MAY, S., PHILLIPS, R., HERMANN, H., AND MUELLER, P.: Bioactivation of Catha edulis alkaloids: enzymatic ketonization of norpseudoephedrine. Biochem. Biophys. Res. Commun. **104:** 38–44, 1982.
97. MCCLURE, D., ARISON, B., JONES, J., AND BALDWIN, J.: Chiral aminoketones from the Friedel-Crafts reaction of protected amino acids. J. Org. Chem. **46:** 2431–2436, 1981.
98. MEREU, G., PACITTI, C., AND ARGIOLAS, A.: Effect of (−)cathinone, a khat leaf constituent, on dopaminergic firing and dopamine metabolism in the rat brain. Life Sci. **32:** 1383–1388, 1983.
99. MORTON, J.: Search for carcinogenic principles. Recent Adv. Phytochem. **14:** 53–73, 1980.
100. MOSSO, U.; Azione fisiologica del principio attivo del Celastrus edulis. Riv. Clin. (Milano) **30;** 65–79, 1891.
101. MUSTARD, M.: Ascorbic acid content of some tropical and subtropical plants and plant products. Food Res. **17;** 31–35, 1952.
102. NELHANS, B.: Khat, a stimulating drug in East Africa and the Arab Peninsula. Research reports of the Department of Sociology, University of Gothenburg, Sweden, **30:** 1–71, 1974.
103. NENCINI, P.: Cathinone, active principle of the khat leaf: its effects on *in vivo* and *in vitro* lipolysis. Pharmacol. Res. Commun. **12:** 855–861, 1980.
104. NENCINI, P., AND AHMED, A.: Naloxone-reversible antinociceptive activity of cathinone, the active principle of khat, in the mouse and rat. Pharmacol. Res. Commun. **14:** 759–770, 1982.
105. NENCINI, P., AHMED, A., AMICONI, G., AND ELMI A.: Tolerance develops to sympathetic effects of khat in humans. Pharmacology **28:** 150–154, 1984.
106. NENCINI, P., AHMED, A., ANANIA, M., MOSCUCCI, M., AND PAROLI, E.: Prolonged analgesia induced by cathinone. Pharmacology **29:** 269–281, 1984.
107. NENCINI, P., AMICONI, G., BEFANI, O., AHMED, A., AND ANANIA, M.: Possible involvement of amine oxidase inhibition in the sympathetic activation induced by khat chewing in humans. J. Ethnopharmacol **11:** 79–86, 1984.
108. NENCINI, P., ANANIA, M., AHMED, A., AMICONI, G., AND ELMI, A.: Physiological and neuroendocrine effects of khat in man. *In* Abstracts, First International Conference on Khat, ed. by International Council on Alcohol and Addictions, pp. 148–152, Lausanne, Switzerland, 1983.
109. NORDAL, A.: Khat: pharmacognostical aspects. Bull. Narc. **32:** 51–64, 1980.
110. NORDAL, A., AND LAANE, M.: Identification of khat. Medd. Nor. Farm. Selsk. **40;** 1–18, 1978.
111. OINUMA, N., WAKASA, Y., AND YANAGITA, T.: Dependence potential of *l*-cathinone. Jpn. J. Pharmacol. **31:** 279P, 1981.
112. PARIS, M., AND MOYSE, H.: Essai de caractérisation du kat, drogue récemment inscrite au tableau B. Annales Pharm. Fr. **15:** 89–97, 1957.
113. QUÉDAN, S.: Catha edulis: Eine wenig bekannte Rausch- und Genussdroge. Planta Med. **21:** 113–126, 1972.
114. QUÉDAN, S.: Uber das ätherische O1 von Catha edulis. Planta Med. **21:** 410–419, 1972.
114a. RADT, C.: Contribution à l'histoire ethnobotanique d'une plante stimulante, le kat au Yémen. J. Agr. Trop. Bot. Appl. **16:** 215–243, 1969.
115. RAMAN, R.: Catha edulis Forsk. Geographical dispersal; botanical, ecological, and agronomical aspects with special reference to the Yemen Arab Republic. Thesis, University of Hohenheim/GFR, 1983.
116. RAYMOND-HAMET, R.: Sur l'action sympathicosthénique d'une Celastracée del l'Afrique orientale, le Catha edulis. Comp. Rend. Acad. Sci. Paris **260:** 1020–1022, 1965.
117. RISNER, M., AND JONES, B.: Role of noradrenergic and dopaminergic processes in amphetamine self-administration. Pharmacol. Biochem. Behav. **5:** 477–482, 1976.
118. ROBERTS, D., AND FIBIGER, H.: Ascending catecholamine pathways and amphetamine-induced locomotor activity: importance of dopamine and apparent non-involvement of norepinephrine. Brain Res. **93:** 441–454, 1975.
119. ROSECRANS, J., CAMPBELL, O., DEWEY, W., AND HARRIS, L.: Discriminative stimulus and neurochemical mechanism of cathinone: a preliminary study. *In* Problems of Drug Dependence. NIDA Research Monograph **27:** pp. 328–329, U.S. Government Printing Office, Washington, DC. 1979.
120. ROSS, S.: The central stimulatory action of inhibitors of dopamine uptake. Life Sci. **24:** 159–168, 1979.
121. SCHECHTER, M., ROSECRANS, J., AND GLENNON R.: Comparison of behavioural effects of cathinone, amphetamine, and apomorphine. Pharmacol. Biochem. Behav. **20:** 181–184, 1984.
121a. SCHOPEN, A.: Das Qat. Research reports of the Department of Ethnology, University of Frankfurt, GFR, ed. by Franz Steiner Verlag, Wiesbaden, GFR, 1978.
122. SCHORNO, X.: Khat, Suchtdroge des Islam. Pharm. Unserer Zeit **11:** 65–73, 1982.
123. SCHORNO, X.: Analytical study on CNS-active phenylalkylamines from khat. *In* Abstracts, First International Conference on Khat, ed. by International Council on Alcohol and Addictions, p. 110, Lausanne, Switzerland, 1983.
124. SCHORNO, X., BRENNEISEN, R., AND STEINEGGER, E.: Qualitative und quantitative Untersuchungen über das Vorkommen ZNS-aktiver Phenylpropylamine in Handelsdrogen und über deren Verteilung in verschiedenen Organen von Catha edulis. Pharm. Acta Helv. **57:** 168–176, 1982.
125. SCHORNO, X., AND STEINEGGER, E.: CNS-active phenylpropylamines of Catha edulis of Kenyan origin. Experientia (Basel) **35:** 572–574, 1979.
126. SCHUSTER, C., AND JOHANSON, R.: Behavioural studies of cathinone in monkeys and rats. *In* Problems of Drug Dependence. NIDA Research Monograph **27:** pp. 324–325, U.S. Government Printing Office, Washington, DC, 1979.
127. SHADAN, P., AND SHELLARD, E.: An anatomical study of Ethiopian khat. J. Pharm. Pharmacol. **14:** 110–118, 1962.
128. SLOVITER, R., DRUST, E., AND CONNOR J.: Evidence that serotonin mediates some behavioural effects of amphetamine. J. Pharmacol. Exp. Ther. **206:** 348–352, 1978.
129. STOCKMAN, R.: The pharmacological action of Catha edulis and its alkaloids. J. Pharmacol. Exp. Ther. **4:** 251–262, 1912.
130. SZENDREI, K.: The chemistry of khat. Bull. Narc. **32:** 5–36, 1980.
131. SZENDREI, K.: Recent progress in khat chemistry. *In* Abstracts, First International Conference on Khat, ed. by International Council on Alcohol and Addictions, pp. 91–109, Lausanne, Switzerland, 1983.
132. TARIQ, N., PARMAR, N., AGEEL, I., AL-MESHAL, I., AND ABU-JAYYAB, A.: The gastric anti-ulcer activity of khat: investigations on its flavonoid fraction. Res. Commun. Subst. Abuse **5:** 157–160, 1984.
133. TSENG, L., AND LOH, H.: Significance of dopamine receptor activity in amphetamine- and methoxyamphetamine-induced locomotor activity. J. Pharmacol. Exp. Ther. **189:** 717–724, 1974.
134. UNITED NATIONS DOCUMENT MNAR/11/1975: Etudes sur la composition chimique du khat; recherches sur la fraction phénylalkylamine, 1975.
135. UNITED NATIONS DOCUMENT MNAR/7/1978. Etudes sur la composition chimique du khat; la configuration absolue de la cathinone, 1978.
136. UNITED NATIONS ECONOMIC AND SOCIAL COUNCIL: Resolution 667 (XXIV)D, document E/3048, 1958.
137. VALTERIO, C., AND KALIX, P.: The effect of the alkaloid (−)cathinone on the motor activity of mice. Arch. Int. Pharmacodyn. Ther. **255:** 196–203, 1982.
138. WAGNER, G., PRESTON, K., RICAURTE, G., SCHUSTER, C., AND SEIDEN, L.: Neurochemical similarities between *d,l*-cathinone and *d*-amphetamine. Drug Alcohol Depend. **9:** 279–284, 1982.
139. WHO ADVISORY GROUP: Review of the pharmacology of khat. Bull. Narc. **32:** 83–93, 1980.
140. WHO Expert Committee on Addiction-Producing Drugs: Khat. WHO Tech. Rep. Ser. **273:** 10, 1964.
141. WINTERFELD, K., AND BERNSMANN, G.: Zur Kenntnis der Inhaltsstoffe von Catha edulis. Arch. Pharm. (Weinheim) **63:** 991–1000, 1960.
142. WOLFES, O.: Uber das Vorkommen von D-nor-iso-Ephedrin in Catha edulis. Arch. Pharm. (Weinheim) **268:** 81–83, 1930.
143. WOOLVERTON, W., AND JOHANSON, C.: Preference in rhesus monkeys given a choice between cocaine and *d,l*-cathinone. J. Exp. Anal. Behav. **41:** 35–43, 1984.
144. YANAGITA, T.: Studies on cathinones: cardiovascular and behavioural effects in rats and self-administration experiments in monkeys. *In* Problems of Drug Dependence. NIDA Research Monograph **27:** pp. 326–327, U.S. Government Printing Office, Washington, DC; 1979.
145. ZEIN, A.: Polydrug abuse among Ethiopian University students with particular reference to khat. *In* Proceedings, International Symposium on Khat, ed. by E. Dagne, Natural Products Research Network for Eastern and Central Africa, Addis Ababa, Ethiopia, pp. 83–89, 1984.
146. ZELGER, J., AND CARLINI, E.: Anorexigenic effect of two amines obtained from Catha edulis in rats. Pharmacol. Biochem. Behav. **12:** 701–705, 1980.
147. ZELGER, J., AND CARLINI, E.: Influence of cathinone and cathine on circling behaviour and on the uptake and release of ^{3}H-dopamine in striatal slices of rats. Neuropharmacology **20:** 839–843, 1981.
148. ZELGER, J., SCHORNO, H., AND CARLINI, E.: Behavioural effects of cathinone, an amine obtained from Catha edulis; comparisons with amphetamine, norpseudoephedrine, apomorphine; and nomifensine. Bull. Narc. **32:** 67–81, 1980.