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MECHANISM OF ACTION OF CATHINONE: THE ACTIVE INGREDIENT OF KHAT *(CATHA EDULIS)*
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ABSTRACT

Objective: **To review the current understanding of the mechanism of action of cathinone, the active ingredient of khat.**
Data source: **Published experimental studies on the nature and action and effect of cathinone on the central nervous system both in animals and humans.**
Data extraction: **Data was taken from work published on the mechanism of action of cathinone and also from work where the action of cathinone and amphetamine was compared.**
Data synthesis: **Data from various studies on cathinone was compared for common themes with regards to its action and similarity with the known mechanism of action of amphetamine.**
Conclusion: **The experimental work shows that cathinone is a liable substance, structually related to amphetamine, and similarly to amphetamine, increases the levels of dopamine in the brain by acting on the cathecholaminergic synaspes. Hence the psychostimulant effect of khat can be accounted for by the mechanism of cathinone, which is considered to be its main active ingredient.**

INTRODUCTION

The habit of chewing khat by the inhabitants of Eastern Africa and Arabian peninsula has a long history. Reference to its use and effects are found in old Arabian literature and in the account of Carten Niebuhrat, an eighteenth century traveller(1). Khat refers to the young leaves and shoots of the plant *Catha edulis* (a species of the Celestracecae family), a flowering evergreen tree or shrub native to regions of eastern Africa and southern Arabia. It has various local names such as *qat* in Yemen, *eschat* in Ethiopia and *miraa* in Kenya. The leaves and shoots are chewed and the juice swallowed which induces a stimulatory and euphorogenic effect in the user. In many societies, khat use has a traditional and culture role in social life, and is used to ward off fatigue and stay alert, similar to the use of cocoa leaves by the inhabitants of Central and parts of South America. For over a century, efforts have been made to isolate the key constituent of khat responsible for its effects. This paper reviews the effect of khat and current understanding of the mechanism of action on the central nervous system (CNS) of its active ingredient, cathinone.

EFFECTS OF KHAT

Khat has been described as a natural amphetamine because its effects are similar to those produced by other known psychostimulants such as amphetamine and its congeners. Alles, Fairchild and Jensen(2) and Hughes(3), after self-consumption of a portion of khat, reported that the effects were similar to a low dose of amphetamine. Like amphetamine, khat, has both peripheral and central nervous system effects. The peripheral effects are mainly sympathomimetic: increase in respiration, body temperature, blood pressure, heart rate and mydriasis. The central nervous system effects are euphoria, alertness, and feeling of well being. In addition, there is insomnia, anorexia, and at high doses, hyperactivity and excessive talking. Psychiatric manifestations such as manic-like behaviour(4) or schizophreniform psychosis(5) or paranoia(6) can occur as a consequence of khat intoxication and are similar to those reported with amphetamine intoxication.

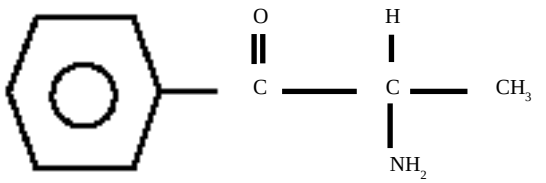
The use of khat often starts at a young age and can develop into a compulsive daily habit lasting a lifetime. It is estimated that there are five to ten million regular khat users(7). The medical and socio-economic impact of khat use on society generates regular, at times heated, debate on whether khat should be considered a drug of abuse and be banned or it should be looked upon as an innocuous stimulant like caffeine conducive to social interaction. The stimulating and euphoric effect of khat can provide a strong inducement for the user to obtain the daily supply and to have long khat chewing periods, especially as tolerance develops with regular use. This strongly suggests development of psychic or physical dependence or both in the user. The World Health Organisation report on khat concluded that khat use may give rise to moderate dependence(8). As the withdrawal signs are minor - lethargy, mild depression, nightmares, and slight tremor(9)- physical dependence is not considered to be a major factor though there appears to be a strong psychic dependency component.

ACTIVE INGREDIENT OF KHAT

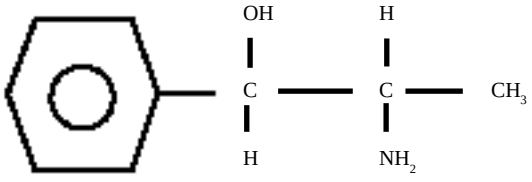
The identity of the active ingredient of khat took sometime to establish. In 1930, Wolfes(10) found the presence of an alkaloid, norpseudoephedrine (cathine), in khat leaves and up to the 1960s this was considered to be the main active ingredient responsible for the effects of khat. However, the amount of cathine in the leaves was insufficient, accounting for only about ten per cent of the CNS stimulation observed(11) and the presence of another compound was suspected. The United Nations Narcotics Laboratory initiated further investigations into the constituents of khat leaves. Fresh and freeze-dried material obtained from Yemen, Kenya and Madagascar were analysed and the presence of a keto analogue of cathine termed cathinone was identified in 1975 (12). Cathinone was found to be a labile substance present mainly in young fresh leaves(13) and its concentration declined rapidly within days after the leaves were removed from the khat tree. The cathinone content was found to vary (0.9-3.3%) according to the country of origin, with khat from Kenya having the highest cathinone content (14). The molecular structure of cathinone was found to be similar to amphetamine (Figure 1). Besides the khatamine or cathedulins group, nearly 20 others compounds have been isolated from khat such as tannins (7-14%), vitamin C (150 mg/100 mg) and trace amounts of thiamine, niacin, riboflavin and carotene.

Figure 1

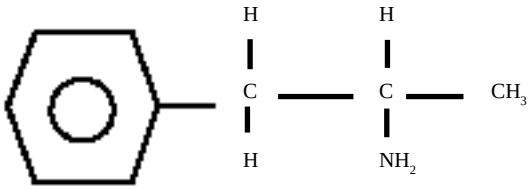
Structure of cathinone, cathine (norpseudoephedrine), and amphetamine



Cathinone



Cathine



Amphetamine

CATHINONE EFFECTS

To determine whether cathinone is responsible for the khat effects, several studies were undertaken. Wilder *et al*(15) compared the effect of fresh and alkaloid-free leaves in six drug naive volunteers. A single dose of khat resulted in plasma cathinone reaching a concentration of 127±53 ng/ml 127±30 min after ingestion of fresh leaves. The Addiction Research Centre Inventory scale, the motor stimulation scale, and the amphetamine-like effect scale were all significant compared to the effect after ingestion of alkaloid-free leaves. The stimulatory effect observed with this dose of khat was similar to a cathinone dose of 0.5 mg/kg body weight. In another clinical experiment, khat effects were assessed in six healthy volunteers given, orally, cathinone corresponding to 100 gm of khat leaves of average cathinone content(16). Evaluation using the questionnaires of the Addiction Research Centre Inventory showed a significant psychostimulant and euphorogenic effect and an increase in blood pressure and heart rate. These changes were coincident with the presence of cathinone (half-life of approximately 1.5 hr) in blood plasma. These studies supported the view that cathinone was the main active ingredient of khat and primarily responsible for its psychostimulatory effect.

Although the effects observed in humans after khat consumption appear to be explained satisfactorily by the action of cathinone, there remained the possibility that other alkaloids could contribute to the khat effect especially cathine. At the peripheral level, cathine has the same sympathomimetic effect as cathinone. However, as pointed out, cathine could not wholly account for the CNS stimulatory effect of fresh khat. First, dry khat leaves do not have the same stimulatory potency as fresh leaves though the cathine content is unchanged. Second, the preference by the khat users for fresh khat rather than old or aged khat suggested that there was something present in fresh leaves which is absent in the old or aged khat. As the cathinone content in fresh leaves decreases rapidly, and from the preference of the user for fresh leaves, it appears that khat user is seeking the effects of cathinone. Furthermore, the lipophilicity of cathinone is greater than cathine which would favour its penetration into the CNS compared to cathine. Thus it would seem that the CNS stimulation of khat is mostly due to cathinone, while the peripheral effects are due equally to the action of cathinone and cathine.

MECHANISM OF ACTION OF CATHINONE

A useful scientific approach to determine if cathinone is responsible for the khat effects is to elucidate its mechanism of action and compare that with the action of other known

psychostimulants such as amphetamine or cocaine. As the structure of cathinone is similar to amphetamine, and khat produces an amphetamine-like effect, most of the investigations have looked at whether the mechanism of CNS action is similar for the two compounds.

Effects of amphetamine are mediated through the release of neurotransmitters at the cathecholaminergic synapses, especially at the dopaminergic and serotinergic synapses.

Kalix(7,17) found cathinone stimulated release of radioactive label from several rat brain regions (nucleus accumbens, striatum and caudate nucleus) prelabelled with ^{3}H-dopamine. These regions are involved in the amphetamine induced hypermotility, a behaviour also observed with cathinone.

Like amphetamine, cathinone has also been found to stimulate release of radioactive label from rat striatal tissue prelabelled with ^{3}H-serotonin. However, compared to amphetamine, cathinone is a third-fold less potent than amphetamine in causing this release(7). Interestingly, the affinity for serotonin receptors by cathinone was found to be about four times higher than amphetamine(18). This finding along with that of Babayai *et al*(19) suggested that activation of the serotonin pathways may have an important role in action of cathinone compared to amphetamine.

BEHAVIOURAL EFFECTS OF CATHINONE

Cathinone has been shown to maintain drug-seeking behaviour in rats habituated to amphetamine and monkeys trained to lever press for cocaine injection(20,21). This indicates that cathinone effects and sites of action have similarity to those of amphetamine and cocaine. Likewise, rats injected with cathinone display the same stereotypical behaviour and hyperlocomotion observed with amphetamines(22). In a further investigation of cathinone induced hyperlocomotion, Calcagnetti and Schechter(22) found that the effect could be produced by injection of cathinone into the third ventricle and the nucleus accumbens region of the brain but not in the substantia nigra. This is in contrast to amphetamine studies which show that substantia nigra is involved in amphetamine mediated hyperlocomotion.

CONDITIONED PLACE PREFERENCE

A useful experimental paradigm widely used to assess motivational properties of drugs of abuse is conditioned place preference. In this approach, the animal learns to associate a particular environment with a drug induced state and another environment with a drug free state. Depending on the effect of the drug, the animal may prefer the environment associated with the drug induced state or have an aversion to it. Drugs that are rewarding or pleasurable will motivate the animal to prefer the drug associated environment while drugs that cause discomfort will have the opposite effect. With this experimental paradigm, many drugs like amphetamines and benzodiazepines abused in humans produce place preference in laboratory animals(24,25). Cathinone also produces place preference in rats both with peripheral and central administration(26) which is inhibited by dopamine antagonists(27). As motivational and reward state is associated with activation of the dopaminergic neuronal system, the place preference produced indicates that, like amphetamine and cocaine, cathinone effects are due to an increase in the dopamine levels in the brain.

STATUS OF KHAT AND CATHINONE

Depending on the country, the status of khat and cathinone varies. In most countries of eastern African and Arabian Peninsula, khat is freely and legally available. In the USA, khat is classified as a Schedule IV substance and cathinone classified as a Schedule I substance by the Drug Enforcement Agency. The United Nation (UN) lists cathinone in the Schedule 1 of the UN Convention on Psychotropic Substances.

TREATMENT OF KHAT ADDICTION

There are very few reports of treatment of khat addition. Gannini *et al*(28) reported two cases of khat dependency which they treated with bromocriptine and desipramine using a protocol developed for cocaine addiction.

NEW DEVELOPMENTS

Since 1991, methcathinone, a derivative of cathinone, has emerged as a new street drug and cheap substitute for methamphetamine in the US. Effects of short term intoxication are similar to crack cocaine or methamphetamine and anecdotal reports from patients in treatment facilities in the US suggest that methcathinone is highly addictive. Data from Russia, where methcathinone abuse has been reported since the 1960's, indicate that many methcathinone addicts suffer permanent brain damage and exhibit Parkinsoniam-like symptoms. Methcathinone is currently on the US Schedule I controlled substances list(29).

In conclusion, khat has a stimulatory and euphorogenic effect in the user. Recent work has lead to the identification of the main active ingredient of khat - a liable alkaloid, cathinone, which appears to be primarily responsible for the effects of khat on the user. A number of studies indicate that the mechanism of action of cathinone is similar to that of amphetamine and involves an increase in dopamine levels in the brain. As most experimental investigations on khat and cathinone have been short term acute studies, there is a lack of important information on the long term effects of khat use, in particular, whether it has the neurotoxic potential.

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