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International Journal of Current Research
Vol. 7, Issue, 11, pp.22587-22590, November, 2015

INTERNATIONAL JOURNAL OF CURRENT RESEARCH

ISSN: 0975-833X

RESEARCH ARTICLE

REVIEW ON KHAT: EARLY FINDINGS ON THE NEUROCHEMICAL AND NEUROBEHAVIOURAL EFFECTS

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ARTICLE INFO

Article History:
Received 28th August, 2015
Received in revised form
26th September, 2015
Accepted 09th October, 2015
Published online 30th November, 2015

Key words:

Amphetamine,
Neurochemical,
Neurobehavioural,
Khat.

ABSTRACT

The stimulant leaf khat (*Catha edulis* Forsk) has been consumed by people living around the horn of Africa, East Africa and the Middle East. It contains many different compounds but its psychostimulant property is mainly related to cathinone which is similar in structure and pharmacological activity to amphetamine. Cathinone is mainly found in the young leaves and shoots. It is expected that the concentration of cathinone determines the market price of khat. Khat must be picked and collected in the morning and chewed as early as possible till that afternoon to preserve maximum potency. Cathinone is absorbed through the mucous membranes of the mouth and subsequently the lining of the stomach. Importantly, since there are no extensive studies on neurobehavioral effect of khat most of the deductions are speculations based on the effect of amphetamine or its derivatives. More importantly, chronic uses of khat associated with brain problems have not been carefully studied. Similar to psychostimulants, khat ingestion produces several central nervous system effects, including increased motor stimulation, euphoria, a sense of excitement and energy. These effects indicate that khat acts through similar central mechanisms as other stimulants. Most of the pharmacological effects of the active principles are suggested to be mediated by the release of biogenic amines such as norephinephrine, dopamine and serotonin.

***Citation*:** Faiz Mohammed, 2015. "Khat: Early findings on the Neurochemical and Neurobehavioural effects", *International Journal of Current Research*, 7, (11), 22587-22590.

INTRODUCTION

KHAT

The stimulant leaf khat (*Catha edulis* Forsk) comes from a tree (of the family Celastraceae) which grows in countries bordering the Red Sea, along the east coast of Africa and in west Asia. *Catha edulis* is popularly known as "khat" but is also known as "kat", "qat", "qad", "qaad". "jaad", and "miraa" (Hoffman and Al'absi, 2010). People living around the horn of Africa, East Africa and the Middle East (Abderrahman and Modallal, 2008; Kimani and Nyongesa, 2008) have consumed it for centuries. Khat chewing is a widespread habit that has a deep-rooted socio-cultural tradition in these countries causing many socio economic problems East (Abderrahman and Modallal, 2008). Khat is chewed for recreational purposes and its valued psychostimulant effect is highest when fresh. These values explain the users' preference for the fresh khat (Kimani and Nyongesa, 2008). Fresh khat leaves mainly contain cathinone, a psychostimulant that is similar in structure and pharmacological activity to amphetamine (Hassen *et al*., 2007; IBRO, 2011; Kimani and Nyongesa, 2008). Due to these similarities, cathinone has been called a 'natural amphetamine' (Connor *et al*., 2002; Hoffman and Al'absi, 2010). It is this psychostimulant effect that accounts for the popularity of khat (Hassen *et al*., 2007).

Many different compounds are found in khat including alkaloids, terpenoids, flavonoids, sterols, glycosides, tannins, amino acids, vitamins and minerals. The phenylalkylamines and the cathedulins are the major alkaloids. Different reports showed that 62 different cathedulins from fresh khat leaves were characterized (ECDD, 2006; Wabe, 2011). In addition to that tannins, vitamin C, α and β sitosterol and friedeline, essential oils, proteins, carotene, calcium, thiamine, riboflavin, niacin and iron are also present in khat (Al-Hebshi and Skaug, 2005).

The khat phenylalkylamines comprise cathinone [S-(–)-cathinone], and the two diastereoisomers cathine [1S, 2S-(+)-norpseudoephedrine or (+)-norpseudoephedrine] and norephedrine [1R, 2S-(–)-norephedrine] (ECDD, 2006; Wabe,

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2011). These compounds are structurally related to amphetamine (Fig. 1) (Al-Hebshi and Skaug, 2005) and noradrenaline. The plant contains the (–)-enantiomer of cathinone only; the (+)-enantiomer is not found. Thus, the naturally occurring S-(–)-cathinone has the same absolute configuration as S-(+)-amphetamine (ECDD, 2006; Feyissa and Kelly 2008; Wabe, 2011).

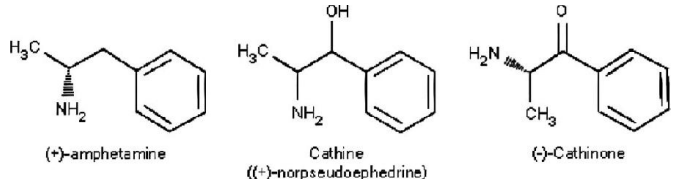

Figure 1. Chemical structures of amphetamine, cathine and cathinone

The pharmacologically active constituents of khat are (-)-cathinone and, to a lesser extent, (+)-norpseudoephedrine (Al-Hebshi and Skaug, 2005; Connor *et al*., 2002). The environment, climate conditions, as well as local traditions connected with cultivation and harvesting determine the chemical profile and general appearance of khat leaves (ECDD, 2006; Feyissa and Kelly 2008; Wabe, 2011). The phenylalkylamine content of khat leaves varies widely (Feyissa and Kelly 2008). Cathinone is mainly found in the young leaves and shoots (Al-Hebshi and Skaug, 2005; ECDD, 2006; Wabe, 2011). It is unstable [in the presence of oxygen, oxidizing at room temperature (Corkery *et al*., 2011), and undergoes decomposition reactions after harvesting and during drying or extraction of the plant material (Al-Hebshi and Skaug, 2005; Al-Motarreb *et al*., 2002; Corkery *et al*., 2011; ECDD, 2006). Cathinone has a more rapid and intense action compared with cathine due to its higher lipid solubility, which facilitates access into the central nervous system (Hassen *et al*., 2007; Kalix, 1988). The stored product loses activity rapidly, becoming physiologically inactive after about 36 h. For the purpose of its maximum potency, khat must be picked and collected in the morning and chewed as early as possible till that afternoon (Corkery *et al*., 2011).

As mentioned somewhere above, cathinone is presumably the main psychoactive component of khat and this explains why fresh leaves are preferred and why khat is wrapped up in banana leaves to preserve freshness (ECDD, 2006; Feyissa and Kelly 2008). It is also reported that the alkaloid fraction may consist of up to 70% of cathinone which is directly correlated with the market price of khat (Feyissa and Kelly 2008). The leaves contain cathine and norephedrine at a ratio of approximately 4:1 (ECDD, 2006; Wabe, 2011). During maturation, cathinone is enzymatically converted to cathine and norephedrine (Connor *et al*., 2002; ECDD, 2006; Feyissa and Kelly 2008). Sunlight and heat induced degradation of cathinone to both cathine and norephedrine also occurs during extraction in the laboratory (Feyissa and Kelly 2008). When khat leaves are chewed, enzymes in the saliva release cathine and cathinone (Al-Motarreb *et al*., 2010). Since chewing is the most common mode of administration, cathinone and cathine are absorbed through the mucous membranes of the mouth and subsequently the lining of the stomach once they are isolated from the leaves by the action of enzymes in saliva while in mouth (Al-Motarreb *et al*., 2010; Hoffman and Al'absi, 2010).

Maximal plasma concentrations of cathinone, after a single oral dose of khat, are attained in about 2 h (Al-Hebshi and Skaug, 2005). The effect of cathinone on the user occurs more rapidly than the effect of amphetamine, roughly 15 min as compared to 30 min (Hoffman and Al'absi, 2010). The terminal elimination half-life is about 4 h (Al-Hebshi and Skaug, 2005). The major metabolite of cathinone is norephedrine, but small quantities of norpseudoephedrine also form (Al-Hebshi and Skaug, 2005; Al-Motarreb *et al*., 2010; Feyissa and Kelly 2008). Less amount of the ingested cathinone (7% or less) appears in unchanged form in the urine. In contrast, cathine and norephedrine are slowly absorbed and then excreted mainly in the unchanged form within about 24 h (Al-Hebshi and Skaug, 2005; Al-Motarreb *et al*., 2010). The fact that cathinone is metabolized to norephedrine can be easily recognized by the amount of norephedrine excreted in urine which is much higher than the amount ingested. Cathine is secreted with breast milk which is experienced by several lactating women who were chewing the leaves of khat (Feyissa and Kelly 2008).

Neurochemical and neurobehavioural effect

Currently most of the deductions that are made about the on neurobehavioral effect of khat are based on amphetamine or its derivatives (Corkery *et al*., 2011). Extensive use of methamphetamines, for instance, has also been repeatedly associated with deficits in episodic memory. Likewise, preliminary observations suggest that chronic use of khat is associated with various cognitive and mental health impairments (Hoffman and Al'absi, 2010). But chronic use of khat associated with brain problems have not been carefully studied (Corkery *et al*., 2011). The deficits seen in chronic methamphetamine users are most evident as impairment in word recall tasks, which measure recall at specific times after stimulus presentation (Hoffman and Al'absi, 2010). Similar to psychostimulants, khat ingestion produces several central nervous system effects, including increased motor stimulation, euphoria, and a sense of excitement and energy (Hoffman and Al'absi, 2010). Khat usage is associated with memory impairment, depression and psychoses (Al-Motarreb *et al*., 2002). It also results in decreased appetite and increased blood pressure and heart rate. These effects indicate that khat acts through similar central mechanisms as other stimulants (Hoffman and Al'absi, 2010). It has been reported that the effects of a portion of khat are very similar to those of about 5-mg amphetamine (Dhaifalah and Šantavy, 2004). Although most of the pharmacological effects of the active principles are suggested to be mediated by the release of biogenic amines through preferential binding to the norepinephrine receptor/transporter, binding to dopamine and 5-HT receptors could also partly contribute to the observed effect (Bedada and Engidawork, 2010).

Cathinone releases catecholamaines from pre-synaptic storage sites resulting in CNS stimulation and a variety of peripheral sympathomimetic effects such as tachycardia and hypertension (Dhaifalah and Šantavy, 2004). For example, both cathinone and amphetamine increase the activity of the dopaminergic and

noradrenergic transmission (ACMD, 2013; Corkery *et al*., 2011; Hoffman and Al'absi, 2010). The sympathomimetic properties are due to peripheral noradrenalin-releasing properties of khat, which potentiate noradrenogenic transmission. It was also found to inhibit neural uptake of noradrenalin (Al-Hebshi and Skaug, 2005)**.** Among the three main khat alkaloids, cathinone is the most potent with regard to induction of release at CNS dopamine terminals. At peripheral sites, however, cathinone, norpseudoephedrine, and norephedrine are about equipotent with regard to induction of release at noradrenergic nerve terminals (Kalix, 1988). Cathinone, like amphetamine, acts by releasing catecholamines (dopamine, serotonin and noradrenalin) from presynaptic storage sites and subsequently inhibit their uptake, thereby increasing the concentration of these neurotransmitters at the presynaptic receptors (Kimani and Nyongesa, 2008). So far there is no clear cut evidence on the role of serotonergic and/or other pathways in the stimulatory effect of cathinone (Feyissa and Kelly 2008).

It has been suggested that cathinone, like amphetamine, releases serotonin in the CNS (Corkery *et al*., 2011; ECDD, 2006; Feyissa and Kelly 2008). Psychostimulants and other drugs that inhibit uptake of 5-HT into the presynaptic nerve terminals increase serotonergic neurotransmission by enhancing its synaptic concentrations (Kimani and Nyongesa, 2008). Some investigators have reported that levels of serotonin in rat brain are not altered by repeated administration of cathinone. Other contrasting evidence could come from a recent study in which both khat extract and cathinone produced a significant depletion of serotonin and its metabolite 5-hydroxyindoleacetic acid in both the anterior and posterior striatum (ECDD, 2006). There are, however, other studies showing that cathinone does not alter levels of serotonin in rat brain following repeated administration (Feyissa and Kelly 2008). Studies in humans showed that serotonin plays a critical role in the pathogenesis of Alzheimer's disease as well as in learning and memory. Dopamine, on the other hand, plays a facilitatory role in cognitive functions, especially those guided by the prefrontal cortex (Kimani and Nyongesa, 2008). Khat extract or cathinone increase the dopaminergic activity by interacting with its pathway (ACMD, 2013; Corkery *et al*., 2011; ECDD, 2006; Kimani and Nyongesa, 2008).

Generally, cathinone is not considered a direct dopamine agonist but rather a presynaptic releaser and re-uptake inhibitor of dopamine (ECDD, 2006)**.** Subsequently, chronic administration of either the whole extract (since both cathine and norephedrine also have effect) or cathinone (100 mg/kg) results in a significant depletion of dopamine in several brain areas, particularly on the nigrostriatal dopamine terminal projections (Feyissa and Kelly 2008; Kalix, 1988). Neurobiological changes due to chronic drug use vary as a function of many factors, including the class of drugs and the pattern of use as well as the complex interplay with preexisting neuro-developmental factors (Hoffman and Al'absi, 2010). Basically, the results reported regarding the neurobehavioral effect of khat extract are not sufficient since there are few studies that are conducted recently in mice. For example, a study made in Kenya showed that acute administration of khat extract had selective effects on both learning and memory (Kimani and Nyongesa, 2008). A study made in Ethiopia by F. Mohammed *et al*. (2014) showed that acute and subacute exposure of mice to khat had no effect on learning and memory although subchronic exposure to khat differentially alters short-term memory without any apparent morphological toxicity in neural processes underlying learning and memory.

This morphometric study, however, did not include morphological changes to the structure of dendrite, axon or synaptic area of neurons. One case history of severe leukoencephalopathy associated with khat misuse has been reported (ECDD, 2006). Earlier Cross-sectional and case-control study in Somalia, in the city of Hargeisa, showed a relationship between khat consumption and onset of psychotic reactions (Odenwald *et al*., 2005). Expermental study carried out in Ethiopia by Bogale and Engidawork (2013) also demonstrated the ability of subchronic exposure of mice to khat to induce schizophrenia-like symptoms that included cognitive decline. Similarly, ECDD (2006) report shows that Khat chewing can induce either a manic illness with grandiose delusions or a paranoid or schizophreniform psychosis with persecutory delusions. Actually, both experimental study in animals and case reports identified that the psychosis symptoms occur at high doses of khat (Alem and Shibre, 1997; Bogale and Engidawork, 2013; ECDD, 2006). The other study on the neurobehavioral effects of khat is related to aggression in which both khat extract and cathinone enhance baseline aggressive behavior of isolated rats (Banjaw *et al*., 2005).

According to the report of F. Mohammed *et al.* (2014) the effect of Khat extract on the wrong decisions seem to be consistent to that obtained with amphetamine and its derivative methamphetamine. Methamphetamine-dependent individuals' exhibit risky decision making and impulse control problems as demonstrated by their sensitivity to immediate versus delayed rewards (Hoffman and Al'absi, 2010). Like amphetamine, khat has also been noted the potential adverse effects on perceptual-visual memory and decision-speed (Corkery *et al*., 2011; ECDD 2006). Other study conducted on chronic amphetamine users also showed disadvantageous decision-making and selected a likely small reward option less frequently than controls (85% of trials versus 95%), which may reflect an impairment in correctly estimating outcome probabilities (Hoffman and Al'absi, 2010).

Even if the study regarding the effect of amphetamine on decision making was made on chronic administration level, it could give an idea to suggest that both amphetamine and khat extract have a disadvantageous effect on decision making. Khat users report that they use this substance to improve their performance, stay alert, increase their energy and to enhance their imaginative ability and capacity to associate ideas, although their concentration and judgment are objectively impaired (Dhaifalah and Šantavy, 2004; Feyissa and Kelly 2008; Hoffman and Al'absi, 2010). Importantly, all of these findings implicate that khat extract does not improve performance or does not enhance imaginative ability and capacity to associate ideas, and does not induce morphological toxicity to the cell body of dentate granules cells, at least, at subchronic level.

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