

Research Article

Khat (*Catha edulis* forsk; family Effect of Khat Habituation on

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Keywords

- Epilepsy
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- Khat (*Catha edulis*)
- Kindling

Abstract

Objectives: Celastraceae) is a plant habitually chewed by several millions of people in Yemen and southern east areas of Africa for its pleasant stimulant effect on physical activity, consciousness, motor and mental functions as well as its anti-fatigue action. This study was aimed to investigate the implication of chronic khat-habituation on secondary generalized seizures in an animal model.

Methods: this study; they were grouped into control, Khat-habituated, and khat-withdrawal. Khat-habituation was induced by providing khat (2g/kg) with food for two months. Khat-withdrawal was induced by cessation of khat-containing food for 14 days. Secondary generalized seizures resemble those occurring in human brain were induced in animals by kindling which was performed by repeated intraperitoneal injection of sub-convulsive doses (11.5mg/kg) of INH at intervals of 30 minutes. The intensity of seizures was determined by empirical scale modified from the behavior scale grading. The latency periods for development of seizures were observed.

Results: Khat-habituated animals showed no epileptic activity all through the experimental period. However, they showed significant decrease in the threshold dose of INH to produce epilepsy, increase in intensity and decrease in latency period of 2ry generalized epileptic seizures induced by INH-kindling. Khat-withdrawal for 14 days reversed effects of khat-habituation on epilepsy.

Conclusion: Chronic khat-habituation in mice resulted in decreased latency period for development of secondary generalized seizures and increased intensity of seizures, this effect may be reversed after its cessation.

INTRODUCTION

Khat (*Catha edulis* forskal, family: Celastraceae) is a plant grown in Yemen and on the eastern coast of Africa [1,2]. The leaves this plant are habitually chewed by several millions of people in Yemen and southern east areas of Africa for its pleasant stimulant effect on physical activity, consciousness, motor and mental functions as well as its anti-fatigue action. The principal active constituents of khat are cathinone and cathine, which have sympathomimetic actions [3].

Epilepsy is chronic neurological disorder characterized by recurrent seizures [4,5]. It is manifested as recurrent attacks of disturbed cerebral function due to hyper-excitability synchronous neuronal activity of cerebral neurons [6]. An imbalance between glutamate and gamma-aminobutyric acid (GABA) neurotransmitter systems can lead to hyper-excitability

but catecholaminergic neurotransmitter systems and opioid peptides were shown to play a role in epileptogenesis as well [7]. In most situations GABA is found in short interneurons, the only long GABAergic tracts being those running to cerebellum and striatum namely the major output of cerebral cortex, olfactory bulb, hippocampus and lateral septal neurons. GABA also mediates inhibition within cerebral cortex and between caudate nucleus and substantia nigra. The latter pathway may mediate decrease in dopamine release [8].

Epilepsy is a public health problem, particularly in tropical developing countries because of its high frequency, acuteness, and its sociological, psychosocial and financial consequences. Hence, the present study aimed to investigate implication of chronic khat-habituation on development and intensity of secondary generalized epileptic seizures which represents the

most common type of epilepsy in human. The study also aimed to assess effect of khat-withdrawal on reversal of khat-habituation effects on epilepsy.

METHODS

This study was carried out in Pharmacology and Therapeutics Laboratory of Faculty of Medicine and Health Sciences, Sana'a University.

Animal

Eighteen adult male mice (*Mus musculus*) weighing 20-30 gm were obtained from the animal house of Faculty of Science of Sana'a University were used for this study. Mice were housed individually in cages, maintained under standard conditions (12 hours light: 12 hours dark cycle; 25 ± 3°C). All animals' procedures were performed in accordance to the institutional Ethics Committee and in accordance with the recommendations for the proper care and use of laboratory animals. The animals were randomly divided into 3 groups consisting of 6 mice in each. Group 1 were normal animals served as "control group". Group 2 "khat-habituation group" were animals received khat in a dose of 2 g/kg body weight for two months. Group 3 "khat withdrawal group" were animals received khat in a dose of 2 g/kg body weight for two months then withdrawn from khat habituation for two weeks. Then, induction of secondary generalized seizures was performed in all these groups by repeated intraperitoneal injection of sub-convulsive doses (11.5 mg/kg) of isonicotinic acid hydrazide (INH) at intervals of 30 minutes "kindling".

Khat-habituation

khat-habituation was induced by providing khat in a dose of 2g/kg with food after an overnight starvation. After one week of forced khat-feeding, the tested animals were provided with both khat-containing and non khat-containing foods. The majority of the tested animals preferred khat-containing food, this model is similar in some aspects the classical self administration model used in testing drug habituation [9,10]. Then, animals showing khat-habituation evidenced by marked preference of khat-containing food were continued to feed khat-containing food in a dose of 2g/kg/day for two months, other animals were excluded from the study due to resistance to khat-habituation. The whole fresh leaves of khat were used in this study because they mostly are used by habituated persons as whole fresh leaves and the dose was adopted empirically to represent an average amount of khat consumed by khat-habituated users, and it was used by many authors from literature.

Kindling

Kindling is the process by which epileptiform activity, perceived as an afterdischarge (AD), can be elicited by applying repetitive subconvulsive electrical or chemical stimulation to structures of the brain and can leads to generalized convulsive seizures [11]. In the present study, secondary generalized epileptic seizures were induced by chemical kindling which was performed by repeated intraperitoneal injection of sub-convulsive doses (11.5 mg/kg) of isonicotinic acid hydrazide (INH) at intervals of 30 minutes.

Determination of intensity of epileptic seizures

Intensity of epileptic seizures in mice was adopted by empirical method modified from the behavior scale grading as described by [12]. This was performed by noticing the mode and duration of epileptic seizures according to the following criteria: **0** = Animal is sleep; **1** = Animal is alert normal active; **2** = Animal is moving (hyperactive); **3** = Animal has partial mild seizure as tremors; **4** = Animal has generalized mild seizure; **5** = Animal has severe seizures, long lasting; **6** = Animal has felt into fatal seizure.

Determination of latency period of epileptic seizures

The average latency periods for development of secondary generalized epileptic seizures in mice induced by INH-kindling were estimated as the duration between the last injections of INH dose till the development of epileptic seizure. The average time was taken and expressed in minutes.

Statistical analysis

Results are presented as mean ± S.E.M. and statistical differences between groups and their respective control for evaluation of experimental results was determined by one way ANOVA using SPSS version 15.0. The level of significance was set at $p < 0.05$.

RESULTS

Effect on Intensity of epileptic seizures induced by INH-kindling

Khat-habituation was associated with significant decrease in the threshold dose of INH to produce epileptic seizures by INH-kindling. This was shown as development of partial seizures in khat-habituated mice after receiving INH dose of 69 mg/kg which induced seizures in khat habituated group. Moreover, the intensity and duration of secondary generalized epileptic seizures induced by INH-kindling showed significant decrease at higher doses of INH compared with khat-habituated mice. These changes were insignificant compared control mice "INH-kindled" (group 1) at either lower or higher INH doses during INH-kindling, which indicates normalization of khat-habituation effect on intensity of epileptic seizures (Figure 1).

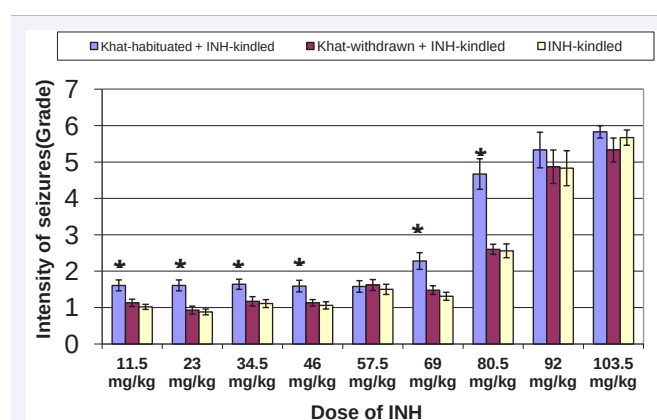


Figure 1 Effect of Khat-habituation (2 g/kg PO for two months) and khat-withdrawal on intensity of epileptic seizures induced by INH-kindling in mice (Scores Mean ± SE, N=6).

*: significant increase of intensity of epileptic seizures compared to both groups.

Khat-habituation was associated with significant decrease in the latency periods for development of secondary generalized epileptic seizures in mice induced by INH-kindling in khat-habituated mice (group 2) at INH doses of 69 mg/kg, 80.5 mg/kg, and 92 mg/kg compared with non khat-habituated mice (group 1). This difference was also significant compared with khat-withdrawal mice at higher doses of INH (Figure 2).

Khat-withdrawal was associated with significant increase in the latency periods for development of secondary generalized epileptic seizures in mice induced by INH-kindling in khat-withdrawn mice (group 3) compared with khat-habituated (group 2) mice. This change was insignificant compared with non khat-habituated mice (group 1) at either lower or higher INH doses during INH-kindling, which indicates normalization of khat-habituation effect on the latency period for development of epileptic seizures (Figure 2).

DISCUSSION

Cathinone and cathine are the principal active constituents of khat, they exert sympathomimetic action by stimulation of catecholamines release (mainly noradrenline and dopamine) from nerve terminals. Cathinone is more lipophilic and pass blood brain barrier more easily than cathine which is more polar compound, so the central effects induced by khat are predominantly due to cathinone and the peripheral effects are due to cathine [3].

Neither of Khat-habituated animals showed any sign of manifest epilepsy. This is in conformation with other studies that showed focal effect of khat on some parts of central nervous system mainly involving limbic system, motor cortex, vomiting center and vasomotor area with no generalized neural activity [3].

The kindling phenomenon proved to be a dominant model for the study of epilepsy once it was demonstrated that spontaneous convulsions can become a permanent behavioral manifestations resembling the genesis and progression of some epileptic disorders [12]. INH is thought to cause seizures by interfering with synthesis of γ -amino butyric acid (GABA) which is the main inhibitory neurotransmitter in the brain by inhibiting glutamic acid decarboxylase enzyme [13].

Khat-habituated animals showed marked augmentation on epileptic seizures induced by INH-kindling. This was evidenced by decrease in the threshold dose of INH to produce epilepsy. Moreover, the latency period required for the development of generalized seizures was decreased and the intensity and frequency of seizures was increased. This may be explained by increased sensitivity of the brain to produce seizure due to cross-sensitization, which means that if a given individual is sensitized by the kindling agent (INH), other different substances may produce altered experience, behavior or function in a stereotyped way [14]. Moreover, there is a site specific augmentation between kindling and khat. This may be represented by the fact that CA3 and CA4 catecholamine secreting neurons of brain stem (in locus ceruleus) are one of the targets of kindling agents. Thus it may be assumed that khat-induced catecholamine release may activate dormant epileptogenic focus or create ectopic focus. Isonicotinic acid hydrazide (INH) inhibited GABAergic interneurons which are the natural defense mechanism against spread of epileptic focus to form generalized epilepsy.

We have found that khat habituation was associated with decreased GABA levels in cerebral cortex, mid brain and hind brain of rodent brain [15]. This was explained by khat habituation increases norepinephrine release through indirect sympathomimetic effect, this released norepinephrine increases the release of GABA as a compensatory response to ameliorate the sympathomimetic effect of khat via either direct stimulation α_1 -receptor [16] or stimulation of α_2 -receptors which disinhibit GABA release inhibitory mechanisms [17]. The released GABA is more liable for glial and neuronal uptake and metabolic degradation which may explain khat-mediated decrease in GABA.

The combined effect of khat in increasing metabolic degradation of GABA as previously mentioned [15], and the effect of isoniazid in decreasing GABA synthesis [14] may explain the deleterious effects on epilepsy. This effect may contribute in the development and progression of secondary generalized and psychomotor epilepsy. GABA secreting neurons in the dentate gyrus received excitatory stimuli from mossy cells in the cerebellum. The former may exert powerful inhibitory influence on the excitatory granule cells of the dentate gyrus. Loss of GABA-secreting cells or dysfunction of mossy cells leads to loss of inhibitory GABAergic control over granule cells. The latter "granule cells of dentate gyrus" may respond by rhythmic synchronous discharge to cortical stimuli and may play a role in conversion of epileptic focus to generalized ictrus [18].

The marked effect of khat-habituation on epileptic seizures was shown at middle doses whereas the effect at higher doses was little; this may be explained by exhaustion of catecholamine stores and appearance of tolerance. Such phenomenon was been observed in indirect and dual acting symapthominetic agents [19].

Khat-withdrawal resulted in amelioration the promoting effect of khat on epilepsy. The intensity and duration of epileptic seizures induced by INH-kindling in khat-withdrawn animals were similar to that of non khat-habituated ones. This may indicate that, khat unlike other indirect-sympathomimetics did not cause long-term structural changes or sensitization of CNS.

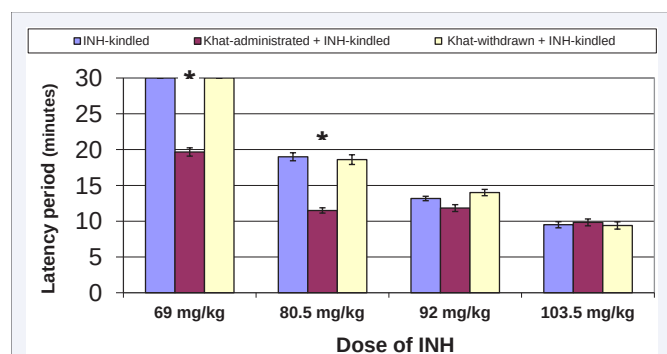


Figure 2 Effect of Khat-habituation (2 g/kg PO for two months) and khat-withdrawal on latency period (time = minutes) of epileptic seizures induced by INH-kindling in mice (Mean $\pm$ SE, N=6).

*: significant decrease of latency period compared to both groups.

CONCLUSION

Chronic khat-habituation in mice resulted in decreased latency period for development of secondary generalized seizures and increased intensity of seizures, this effect may be reversed after its cessation. Chronic khat habituation has transient deleterious effect on the development and spread of epilepsy which may be reversed after its cessation.

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