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Effect of Khat habituation on psychomotor behavior in mice

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ABSTRACT

Objectives: The present study was aimed to investigate the effect of khat-habituation on psychomotor behavior in mice and the effect of khat withdrawal on reversal of khat habituation effects. **Methods:** Eighteen adult mice (20-30 gm) were used in this study. The animals were grouped into 3 groups, including one group served as control. Khat-habituation was induced by providing khat in a dose of 2 g/kg with food after an overnight starvation, after one week, the tested animals were provided with both khat-containing and non khat-containing foods and the majority of the tested animals preferred khat-containing food. The animals which preferred khat-containing food were regarded as showing khat-habituation and were continued to feed khat-containing food in a dose of 2g/kg/day for two months to develop chronic khat habituation, animals which had not preferred khat-containing food were excluded from the study and were regarded as resistant to khat habituation. Khat-withdrawal was induced by feeding animals with food without khat for a period of 14 days. Locomotor activities of animals were noticed and determined according the behavior scale grading to assess the effect of khat-habituation on locomotor activity, and khat-withdrawal on reversal of khat-effects. **Results:** Khat-habituated animals showed significant increase in stereotypic psychomotor behavior maximally reached 15-30 minutes after khat consumption. Khat-withdrawal for 14 days was associated with normalization of psychomotor behavior in mice. **Conclusion:** Chronic khat-habituation has a prominent increase in psychomotor behavior in mice; this effect is transient and can be reversed by after its cessation.

Keywords: Khat (*Catha edulis*), Psychomotor behavior, Locomotor activity

1. Introduction

Khat (*Catha edulis* Forskal, family: Celastraceae), a flowering evergreen shrub to small tree growing up to 10 m tall cultivated in East Africa and the South-West Arabian Peninsula including Yemen^[1,2]. Khat leaves and fresh shoots are chewed regularly by several millions in these countries for their for its pleasant stimulant effect on physical activity, consciousness, motor and mental functions as well as its anti-fatigue action.

The principal active components in khat are cathinone and cathine which have indirect sympathomimetic activity by stimulating release of endogenous catecholamines from nerve terminals. Both have amphetamine-like effects and the pharmacological actions of cathinone are qualitatively similar to those of amphetamine, although it is less potent. Chewing khat releases these substances into the saliva then they are rapidly absorbed and eliminated. Cathinone is characterized by its greater lipophilicity and pass more easily into central nervous system than cathine which is less lipophilic, so the central effects induced by khat can be considered to be predominantly due to cathinone while the peripheral effects are due to cathine^[3]. Fresh leaves are preferred to be chewed, because cathinone is labile and transformed within a few days of harvesting to a dimer in the old or dry plant material.

Although, Khat is not under International control but is scheduled by some Member States. Cathinone and cathine are listed in the 1971 United Nations Convention on Psychotropic Substances under Schedules I and III respectively. The chewing of khat is common and has a deep-rooted social and cultural tradition in Yemen and has been associated with several socioeconomic and health burdens. The present study aimed to investigate the effect of khat-habituation on psychomotor behavior in mice. The study also aimed to assess effect of khat withdrawal on reversal of khat effects on psychomotor behavior.

2. Methods

This study was performed in the department of Pharmacology and Therapeutics, Faculty of Medicine and Health Sciences, Sana'a University, Yemen.

2.1 Animals:

Eighteen adult male mice (20-30 g) obtained from the animal house of Faculty of Science of Sana'a University were used for this study. 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, unnecessary procedures were avoided. Mice were maintained under standard conditions (12 hours light: 12 hours dark cycle; 25 ± 3 °C). The animals were randomly divided into 3 groups consisting of 6 mice in each. Group 1 (control group) were normal animals served as control Group 2 (khat-habituation group) were animals received khat in a dose of 2 gm/kg for two months. Group 3 (khat withdrawal group) were animals received khat in a dose of 2 g/kg for two months then withdrawn from khat consumption for two weeks.

2.2 Khat-habituation:

khat-habituation in mice was induced by adopting model similar in some aspects the classical self-administration model used in testing drug habituation [4,5]. In this model Khat was provided to animals in a dose of 2g/kg with food after an overnight starvation, after one week, the tested animals were provided with both khat-containing and non khat-containing foods and the majority of the tested animals preferred khat-containing food. The animals which preferred khat-containing food were regarded as showing khat-habituation and were continued to feed khat-containing food in a dose of 2g/kg/day for two months to develop chronic khat habituation, animals which had not preferred khat-containing food were excluded from the study and were regarded as resistant to khat habituation. Khat-withdrawal was induced by feeding animals with food without khat for a period of 14 days. In this study, whole fresh young leaves of khat plant were used as they are the mostly the parts of the plant ingested by habituated users. The dose of

2g/kg/day of fresh leaves was adopted empirically to represent the average amount of khat consumed by habituated persons, this dose also has been used by many authors from literature.

2.3 Determination of psychomotor behavior in mice:

Locomotor activity in mice was determined by the behavior scale grading as described by Quinton and Halliwell [6]. This was performed by noticing the motor activity of mice and giving scores for their movements according to the following criteria: **0** = Animal is sleep; **1** = Animal is alert but not moving; **2** = Animal is moving around the cage (hyperactive); **3** = Animal shows stereotyped sniffing at bars; **4** = Animal is licking bars; **5** = Animal is (mock) biting (momentary touching bars with teeth); **6** = Animal is growing bars of floor or wall of the cage. The average score of motor activity of mice was taken for 10 minutes after half an hour of khat-consumption during 3 consecutive days after 2 months of khat-habituation in (group 2) and after 14 days of khat-withdrawal (in group 3).

2.4 Statistical analysis:

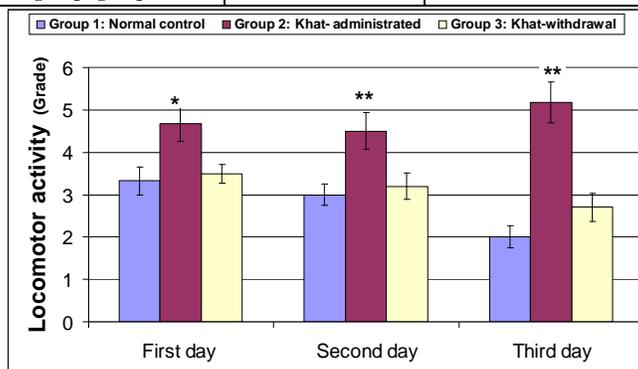
Results are presented as mean \pm S.E.M. and statistical differences between experimental groups was determined by one way ANOVA using SPSS version 15.0.

3. Results:

Observation of psychomotor behavior of mice showed significant increase in khat-habituated mice (group 2) scores compared with normal control mice (group 1) which had not been received khat, this was manifested in the form of prominent stereotypic movements. The time course of locomotor movements was maximal after 15-30 minutes of khat-consumption; it appeared at steady increase during the experimental period starting from the third day and then reaches steady state (Table 1, Figure 1). Khat-withdrawal was associated with significant decrease in psychomotor behavior of mice starting from the third day and reaching steady state after about one week.

Table 1: The effect of Khat-habituation (2 g/kg PO for two months) and Khat-withdrawal (for 14 days) on psychomotor behavior (locomotor activity) during 10 minutes for 3 consecutive days in mice (Scores Mean \pm SE, N= 6):

| Group | Locomotor activity (Scores Mean \pm SE) | | |
|------------------------------------|---|----------------|-----------------|
| | First day | Second day | Third day |
| Normal control group (group 1) | 3.33 \pm 0.33 | 3 \pm 0.26 | 2 \pm 0.26 |
| Khat-administrated group (group 2) | 4.67 \pm 0.42 | 4.5 \pm 0.43 | 5.17 \pm 0.48 |
| Khat-withdrawal group (group 3) | 3.5 \pm 0.22 | 3.2 \pm 0.31 | 2.7 \pm 0.33 |



*: significant increase in locomotor activity compared to both groups at $P \leq 0.05$.

** : significant increase in locomotor activity compared to both groups at $P \leq 0.01$.

Fig 1: The effect of Khat-habituation (2 g/kg PO for two months) and Khat-withdrawal (for 14 days) on psychomotor behavior (locomotor activity) during 10 minutes for 3 consecutive days in mice (Scores Mean \pm SE, N= 6):

4. Discussion

The principal active constituents of khat are cathinone and cathine, which have sympathomimetic actions. They facilitate neurotransmission by stimulating the release of catecholamines (mainly dopamine and noradrenalin) from presynaptic sympathetic nerve terminals. Cathinone is characterized by its greater lipophilicity and pass more easily into central nervous system than cathine which is less lipophilic, so the central effects induced by khat can be considered to be predominantly due to cathinone while the peripheral effects are due to cathine^[3].

In this work, the reinforcement behavior that encouraged continuous khat consumption (Khat-habituation) in mice may be mood elevation, increase motor activity and resistance to fatigue. This assumption is supported by the preliminary study of Van der Schoot^[7] who found that cathinone – one of the active principles of khat – has about half the potency of amphetamine in increasing the spontaneous locomotor activity in mice. Cathine, the other active principle of khat, has one tenth of potency of amphetamine in increasing the locomotor activity in mice^[8]. The stimulant effect of khat was also observed in monkey which showed marked restlessness and resistance to fatigue after self-administration of cathinone^[9].

The time course of locomotor effects of cathinone was maximal after 15-30 minutes. It was comparable in potency but shorter in duration than the other active principle of khat namely cathine. Cathinone has potency comparable to dextroamphetamine in increasing locomotor activity. It has more prolonged effect. The maximal effect of cathinone is 90-120 minutes^[10].

The motor stimulant effect of khat may be attributed to the effect of khat in increasing the concentration of monoamines namely norepinephrine, dopamine and serotonin in relevant areas of the brain. This was evidenced by the work of Valterio and kalix^[11] who showed that cathinone induced locomotor behavior could be prevented by pretreatment with dopamine antagonists for example haloperidol, spiroperidol and pimozide. This may imply that the stimulant effect of cathinone involves, as that of amphetamine, activation of dopaminergic pathways. Furthermore, depletion of monoamines by prior reserpination (administration of reserpine) partially inhibited the stimulant effect of cathinone^[12]. Such effect in reserpined mice was prevented by either monoamine reuptake inhibitors namely Nomifenisne and Mazindole^[11] or catecholamine synthesis inhibitors namely α -amino-para-tyrosine.

Khat-habituated animals showed psychomotor behavior in the form of prominent stereotypic movements compared with control animals (non khat-habituated). This may reflect increased sensitivity of tested animals to external stimuli^[5]. The mechanism of khat-induced stereotypic behavior may be attributed to increase in dopamine rather than serotonin release. Connor *et al*^[13] demonstrated that cathinone-induced spontaneous motor behavior in mice was blocked by dopamine receptor blockers e.g. haloperidol rather than serotonin receptor blockers e.g. Methysergide. In vivo microanalysis experiments have shown that cathinone and amphetamine increased extracellular dopamine concentration in the neostriatum of rat more than in other dopamine containing brain areas^[14]. This may imply that neostriatum is the site of action of cathinone mediated stereotypic behavior.

5. Conclusion

Chronic khat-habituation has a prominent increase in psychomotor behavior in mice; this effect is transient and can be reversed by after its cessation.

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