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Effects of Chronic Khat Use on Cardiovascular, Adrenocortical, and Psychological Responses to Stress in Men and Women

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Abstract

Background: Khat is a psychostimulant plant widely used in Africa and its use has been growing rapidly in Europe and North America.

Objectives: We investigated effects of chronic khat (*Catha edulis*) use on cardiovascular, adrenocortical, and psychological responses to acute stress.

Methods: Chronic khat users and nonusers were compared on physiological measures and mood reports in a cross-sectional, mixed design. Measurements were conducted during 24-hour ambulatory monitoring and during a laboratory session. A total of 152 participants (58 women) were recruited by flyers posted around Sana'a University campus and the surrounding community in Sana'a, Yemen. Salivary cortisol and self-report measures were collected during a 24-hour ambulatory period prior to a lab testing session. In addition, blood pressures (BP), salivary cortisol, and mood measures were assessed during rest and in response to acute mental stress.

Results: Khat users exhibited enhanced evening and attenuated morning cortisol levels, reflecting a blunted diurnal pattern of adrenocortical activity compared to nonusers. Khat users reported greater negative affect during the ambulatory period and during the laboratory session. In addition, they exhibited attenuated BP responses to stress.

Conclusions and Scientific Significance: These novel results demonstrate altered adrenocortical activity and increased dysphoric mood among khat users. The extent to which these associations are due to effects of chronic khat use per se or instead reflect predisposing risk factors for khat use is yet to be determined.

INTRODUCTION

Recent reports indicate a dramatic rise in the prevalence of substance use in developing countries, increasing the threat of grave consequences for population health and compromising sustainable economic development.^{1,2} The situation is unique in populations

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Declaration of Interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

where endogenous stimulants are readily available and widely used. The impact of exposure to these substances may be particularly devastating in low income countries where effects of drugs are complicated by other hardships, including malnutrition, poverty, limited and poor quality water resources, and inadequate health care.^{1,3}

Khat (*Catha edulis*) is a tree which grows at high altitudes in an area extending from East to Southern Africa, parts of the Middle East, and on the island of Madagascar.^{4–6} The leaves of the khat tree are chewed for their psychostimulant properties. Khat chewing has a social and cultural tradition, as it usually occurs while in the company of others.⁶ Khat use has been growing in Western Europe and North America among immigrant communities.⁷ Although khat historically has been used for medicinal purposes,^{6,8} it is most valued for its stimulant effects.⁹ Khat use is legal in some countries in Africa and Europe, but is illegal in others. Chewing khat leaves is the most common mode of administration,⁶ and it is usually chewed “fresh” during afternoon sessions that last 2–5 hours.¹⁰

Reported acute effects of khat include increased levels of alertness, ability to concentrate, confidence, friendliness, contentment, and flow of ideas.^{6,11} Following the acute effect phase, khat users usually report feeling one or more of the following: dysphoria, lethargy, numbness, insomnia, or fatigue. The major pharmacologically active constituent of khat is cathinone, an amphetamine-like sympathomimetic amine.^{9,12} In placebo-controlled studies, khat has been found to increase motor activity, euphoria, and a sense of excitement and activation.^{9,13} Recent studies have demonstrated an association of khat with increased sympathetic activity^{12–15} and clinical observations suggest increased risk for acute myocardial infarction and stroke.^{16,17} Cathinone suppresses appetite, increases dopamine and norepinephrine, and is associated with sympathetic activity.¹⁸ These results indicate that acute effects of the cathinone in khat are similar to those of amphetamine, although at a lower intensity.

Although harm to human physical health caused by khat has long been recognized,^{19,20} there is very little research addressing its effects on human behavioral functions and emotion regulation, either acutely or chronically. This knowledge is critical in understanding the neurobehavioral effects of khat use and for guiding efforts to address the escalating use of khat and its adverse health consequences. This study was conducted to investigate effects of chronic khat use on physiological, adrenocortical, and psychological responses to acute stress by comparing chronic khat users with a control group of nonusers. Responses to stress reflect the ability to both regulate emotions and respond to acute demands.^{21,22} Blood pressures (BP), salivary cortisol, and mood measures were assessed during rest and in response to acute stress in a laboratory setting. The study included men and women to examine gender differences. Based on literature related to other psychostimulants,^{23–25} our hypothesis was that chronic khat use would be associated with dysregulated responses to acute stress, characterized by blunted physiological responses and enhanced negative affect.

METHODS

Participants

Participants were recruited using flyers posted around the Sana'a University campus and in the surrounding community in Sana'a, Yemen. Participants were eligible for the study if they were free from any medical conditions and were not taking any medications. Khat users had to have been chewing khat on a daily basis for at least 2 years. Nonusers should have never been regular users and should have not used khat even once over the recent 2 years. All sessions for the study were conducted at Sana'a University between 2006 and 2008. Participants signed a consent form approved by the local Institutional Review Board of Sana'a University, and they received a small monetary incentive for completing the study.

Apparatus and Measures

Self-Report Measures—A subjective state measure that has been translated and used in the country was used here to assess mood states during ambulatory and laboratory sessions. The Subjective State Measure included 18 items that have been translated from previous adjective checklists used in laboratory experiments and found to be sensitive to acute mood changes.^{26–28} These rating items cover negative affect, positive affect, and physical symptoms. The Cronbach's α values for negative affect, positive affect, and physical symptoms were .85, .79, and .82, respectively. This measure was completed during the ambulatory period and before and after performing an acute stress challenge.

Physiological Measures—Saliva samples were collected in this study to measure cortisol. Participants received specific instructions concerning collection and storage of samples. The use of salivary cortisol was well suited for this study to accommodate the limited local research capacity. Samples were stored in -20°C until assay. Salivary cortisol was assayed using a chemiluminescence immunoassay assay (CLIA) with sensitivity of 16 ng/ml (IBL-International, Hamburg, Germany). Intra- and inter-assay coefficients of variation were below 6%.^{29,30} BP and heart rate measures were collected using a MicroLife Automatic Blood Pressure Monitor BP 3AC1 attached by an inflatable cuff to the subject's left upper arm. This is an oscillometric device that has been validated by the European Society of Hypertension's international protocol. The advantages of such automated units are reliability and freedom from differences in auscultatory practices between operators.

Procedures

Participants attended a screening session to assess eligibility for the study and availability to participate in all phases of the protocol. The screening session included assessment of current and history of khat use as well as the use of tobacco and other substances. Participants also completed forms and questionnaires related to behavioral health and stress. A set of dietary guidelines and instructions about sleep were provided to the participants prior to ambulatory and laboratory sessions. On the day prior to the laboratory session, participants reported to the laboratory between 10:00 am and 12:00 pm. They were supplied with a set of saliva sample tubes as well as monitoring and mood ratings forms to be completed during the following 24 hours. Participants were instructed to collect salivary samples at 10:00 am, 7:00 pm (cortisol nadir level), 10:00 pm (before going to bed), on the

next day at 8:00 am (after waking up; morning sample), and then again at around 9:00 am. Participants were asked to indicate any coffee consumption and food intake, every time they collected a saliva sample. They also completed the locally translated version of the Subjective State Measure, as described above.³¹

Testing in the laboratory started between 9:00 and 10:00 am. At the beginning of each session participants answered questions about their diet and verified continuous eligibility (ie, participant was still in good health and not taking any medications). Subjects then sat in a comfortable chair, and the BP cuff was attached. Participants rested for 30 minutes. This was followed by instructions and exposure to an acute stressful challenge for 10 minutes, followed by a recovery rest period of 15 minutes. The acute challenge was a mental arithmetic task that involved subtraction of the number 7 or 13 from a four-digit number. Participants were asked to perform as fast as they could. When a mistake was made, the participant was asked to go back to the previous correct number. This task has been previously used in multiple stress reactivity studies.^{26,27} BP and heart rate were measured during rest, the acute stressor, and recovery period. Rate pressure product (RPP) (mmHg/min, calculated as HR systolic BP) was included as an index of myocardial oxygen demand. Measures were obtained every 3 minutes during the acute stressors and every 5 minutes during the baseline and rest recovery periods. Salivary cortisol samples were collected after baseline rest, after the stressor, and after the recovery period. Subjects also completed a mood state measure at these times.

Data Analysis

Age, education, body mass index (BMI), and average sleep (hours/night) were compared across groups (khat users, nonusers) using one-way ANOVAs. Mixed model repeated measure ANOVAs were used to analyze physiological and self-report data. These analyses included two between-subject factors: Group (khat users, nonusers) and Gender, and one within-subject factor (Sampling Time). Analyses were conducted on the data obtained from the laboratory session and the ambulatory measure results separately. The analyses on the 24-hour data were based on 2 Group (khat users, nonusers) $\times$ 2 Gender $\times$ 5 Sampling Times. Laboratory session data were analyzed using 2 Group (khat users, nonusers) $\times$ 2 Gender $\times$ 3 Sampling Times (baseline rest, immediately after stress, and after recovery rest). To maximize the reliability of the results, cardiovascular measures were averaged across three periods (baseline, stress, and recovery periods) and similar models were used with these measures. Additionally, cardiovascular responses to acute challenge were also defined using change scores (task value minus the baseline value), and analyses comparing the groups on these changes were conducted. Due to the variable numbers of missing data, variations existed between sample size and degrees of freedom for the reported variables. All repeated measure ANOVA models were conducted using SAS software, version 9.2 procedure PROC MIXED using an unstructured covariance matrix. We included data from a total of 152 participants, although some of the measures were incomplete in a portion of the samples as indicated below. Completed self-report measures from the ambulatory period and laboratory testing session were available from 148 participants. Completed cardiovascular measures obtained during the laboratory session were available from 134 participants. Completed

measures for salivary cortisol samples across the ambulatory and laboratory testing measures were available from 109 participants.

RESULTS

Participant Characteristics

Table 1 includes demographic characteristics of khat users and nonusers. Groups were similar in BMI and years of education, but age and average sleep differed between khat users and nonusers, and female khat users had a greater average BMI than any of the other groups ($F(1, 126) > 4.38, p < .05$). Pearson correlations did not show any significant association between age, average sleep, and any of the cardiovascular and self-report measures. Age correlated with cortisol levels ($r = -.21; p < .05$); however, analysis of cortisol results using age as a covariate did not yield significant effects of age in the model ($F(1, 117) < 1$).

Self-Report Measures

Ambulatory Assessment—As seen in Figure 1, khat users reported greater negative affect compared to nonusers ($F(1, 144) = 8.87; p < .01$). There was a Sampling Time effect ($F(4, 144) = 4.66; p < .01$), with a significant reduction in negative affect scores from evening to morning. There was also a significant Group $\times$ Time interaction ($F(4, 144) = 2.61, p < .05$). This was due to significant changes across time in khat users ($F(4, 144) = 5.01, p < .001$) but not in nonusers ($F < 1$). Men reported more positive affect than women ($F(1, 144) = 10.99; p < .01$), and nonusers reported greater positive affect than khat users ($F(1, 144) = 10.45; p < .01$). Khat users reported more physical symptoms than nonusers ($F(1, 144) = 15.21; p < .0001$). There was also a significant decrease in reported physical symptoms from evening to morning in both groups ($F(4, 144) = 3.87; p < .01$).

Laboratory Assessment—Khat users reported greater negative affect than nonusers across all times during the laboratory session ($F(1, 144) = 5.78; p < .05$; see Fig. 2). Stress was also associated with increase in reported negative affect ($F(2, 144) = 5.28; p < .01$). There was a significant Group $\times$ Time interaction ($F(2, 144) = 3.66, p < .05$), reflecting significant increases in negative affect in response to stress in khat users ($F(2, 144) = 6.77, p < .01$) but not in nonusers ($F < 1$). Khat users reporting less positive affect than nonusers ($F(1, 144) = 8.17; p < .01$), and men reporting more positive affect than women ($F(1, 144) = 5.32; p < .05$). During stress, reported positive affect was reduced, as evidenced by a Time main effect ($F(2, 144) = 10.66; p < .0001$). Khat users reported greater physical symptoms than nonusers ($F(1, 144) = 9.09; p < .01$). None of the other main effects and interactions related to this measure were significant ($F_s < 1.36$ and $p_s > .26$).

Cortisol Concentrations

Ambulatory Assessment—There was a main effect of Sampling Time ($F(4, 105) = 56.04; p < .0001$), reflecting the marked increase in cortisol levels from evening to morning. There was also a main effect of Group showing increased cortisol concentrations in khat users compared to nonusers ($F(1, 105) = 4.66, p < .05$). This was, however, qualified by a Group $\times$ Sampling Time interaction ($F(4, 105) = 4.46; p < .01$) as well as a Group $\times$ Gender $\times$ Sampling Time interaction ($F(4, 105) = 2.9; p < .05$), and a Gender $\times$ Sampling Time

interaction ($F(4, 105) = 4.09$; $p < .01$); Fig. 3. Khat users had higher cortisol levels than nonusers during early evening, but blunted cortisol levels in the morning. Female nonusers had higher increases in cortisol levels from the evening to the morning compared to female khat users ($F(1, 100) = 9.79$; $p < .001$). However, there was no difference between male khat users and male nonusers.

Laboratory Assessment—Examining the three cortisol samples obtained during the laboratory session, we found a main effect of Sampling Times ($F(2, 105) = 5.42$; $p < .01$). This was due to a significant reduction in cortisol concentrations after the recovery period. Follow-up analyses examining cortisol levels obtained before and after the stressor resulted in a marginal Group $\times$ Time interaction ($F(1, 104) = 3.22$; $p < .08$), reflecting a trend towards attenuated cortisol levels following the stressor in khat users.

Measures During the Laboratory Session

Figure 4 depicts results of the cardiovascular measures. Systolic BP increased significantly in response to stress, as indicated by a significant Time main effect ($F(2, 130) = 14.99$; $p < .0001$). Diastolic BP also increased significantly in response to stress ($F(2, 130) = 15.23$; $p < .0001$). There was a significant Group $\times$ Time interaction ($F(2, 130) = 3.50$; $p < .05$). Nonusers had higher diastolic BP levels than khat users during stress ($F(1, 130) = 4.17$; $p < .05$). However, there were no group differences at baseline and recovery periods ($F_s < 1$).

A significant main effect of Time was found for heart rate, reflecting the significant increase in response to stress ($F(2, 130) = 19.75$; $p < .0001$). There was also a main effect of Gender, with women exhibiting higher heart rate than men ($F(1, 130) = 4.61$; $p < .05$). This was, however, qualified by a significant Groups $\times$ Gender interaction ($F(1, 130) = 9.42$; $p < .01$). The interaction was due to higher heart rate in female nonusers compared with male nonusers ($F(1, 130) = 18.03$; $p < .0001$), but no such difference was found in khat users. RPP increased significantly during the stressor in all participants [main effect of Time; $F(2, 130) = 32.63$; $p < .0001$].

Correlation Analyses

To further assess the relationship between cortisol concentrations, cardiovascular responses, and self-report measures, we conducted a series of Pearson correlation analyses within the khat user and nonuser groups separately. In nonusers, cortisol levels during the laboratory session consistently correlated with reported negative affect ($r_s = .29$ – $.34$, $p_s < .05$). None of these correlations was significant in khat users ($r_s < .03$). The correlation coefficients differed between the two groups ($Z = 2.26$; $p < .05$; see Fig. 5). Similar patterns were found with reported physical symptoms. While cortisol concentrations correlated with physical symptoms during the laboratory session in nonusers ($r_s = .33$ – $.45$; $p < .05$), no such correlations were found in khat users ($r_s < .01$). The correlation coefficients in the two groups differed significantly ($Z = 3.37$; $p < .0001$; Fig. 5). Systolic and diastolic BP as well as RPP correlated with positive affect in nonusers ($r_s > .24$; $p_s < .05$), but not in khat users.

DISCUSSION

This is the first study to examine effects of chronic khat use on psychophysiological and adrenocortical activity and examine gender differences among khat users. There were three primary findings of the study. First, khat users exhibited enhanced evening and attenuated morning cortisol levels, reflecting a more flattened diurnal pattern of adrenocortical activity compared to nonusers. Second, khat users reported more negative affect during the ambulatory monitoring period and in response to the laboratory stressor compared to nonusers. Third, khat users exhibited blunted BP responses to stress compared to nonusers.

Cortisol production has a clear diurnal variation^{32,33} with the peak activity of cortisol occurring about 8:00 am with a normal sleep pattern, followed by steady decline until noon. The time selected for cortisol sampling was optimal for assessing the diurnal effect and provided the best chance to observe any alternations in the pattern. The study documented a flattened diurnal pattern of cortisol release in khat users relative to nonusers. This pattern resembles that previously observed in other substance use populations, such as smokers and cannabis users^{24,34–36} suggesting disruption in circadian functions among khat users.

The diurnal pattern obtained here is similar to that seen in individuals with depression and childhood trauma.^{25,37,38} It is possible that chronic activation of the hypothalamic–pituitary–adrenocortical (HPA) axis associated with depression and trauma leads to long-term allostatic changes manifested by hyporesponsiveness to stress and flattened diurnal pattern.^{39–41} Due to their chronic, ongoing khat use, it is possible that results from khat users reflect these long-term changes. The findings of enhanced negative affect level among khat users indirectly confirms the possibility that dysphoric mood may also be linked to cortisol dysregulation. It was also intriguing to find that associations between cortisol concentrations and negative affect were only significant in nonusers, suggesting the possibility that discordance between this stress hormone and mood state reflects disruption in peripheral expression of central emotion regulation processes.

The specific neurobiological mechanisms responsible for the pattern of adrenocortical and self-report measures obtained here are not known at this time, but most likely involve multiple systems. Similar to other psychostimulants, it is possible that chronic use of khat impacts several central functions related to dopaminergic, adrenergic, opioid, and HPA axis activity.^{11,42–45} Chronic exposure to khat and its constituents, such as cathinone and cathine, may lead to receptor and synaptic related changes in multiple regions of the brain, including the paraventricular nucleus and the locus coeruleus.^{43,46–49} To this end, it is possible that regular khat use is associated with an ongoing activation that would be associated with enhanced basal HPA activity but reduced responses to challenges, such as the adrenocortical increase after awakening that has been used as a marker of adrenocortical functional status.^{50,51}

We note that there were only marginal differences between users and nonusers during the laboratory session, showing decline in cortisol concentrations among khat users following the stressors. Cortisol concentrations, however, did not increase significantly following the stressor in either group, although the normal diurnal pattern of the cortisol release during the

time of the experiments would have been lower. A control rest-day session could have demonstrated the effects of the stressor more clearly than examining changes within the same session.⁵² We do consider, however, the possibility that the brief stressor used here may have not been challenging enough to produce significant adrenocortical responses. The tendency to exhibit attenuated responses to stress is consistent with previously observed results in smokers and other substance using populations^{24,34,35,53} possibly reflecting long-term alterations of central stress and reward-related systems.^{54,55}

The present study systematically examined variables that may mediate effects of chronic khat use or are associated with these effects on affect and physiological regulation. Previous studies have attempted to address chronic effects of khat on various physical and psychological functions. These studies have been limited by the restriction of small sample sizes or single case studies, the recruitment of male khat users only, the absence of a control nonusing population, and a reliance on rudimentary self-report measures. Nevertheless, these studies have consistently suggested long-term effects of khat on psychological functions ranging in severity from minor (eg, insomnia, anxiety, irritability, agitation, and aggression) to major psychiatric problems including psychotic disorders and mania.^{8,56–59} The current study provides more proximal measures related to the chronic effects of khat use and identifies potential mediators linking khat use with long-term effects on neurobehavioral functions and psychological problems. Furthermore, the results suggest that adverse effects of khat use are similar in men and women. These results support the importance of focusing on khat use in women in light of observations indicating increased khat use among this group, including khat use during pregnancy.⁶⁰

We note that this study was limited by the lack of an objective measure of khat use and the use of the limited stress battery during the laboratory session. This study, however, had several strengths including the use of multiple physiological measures in a controlled setting to examine the effect of stress. The study was the first to carefully examine diurnal cortisol release among khat users and to address effects of khat use on these measures in women. It included a relatively large sample size, a control group of nonusers, and an adequate sample of women to permit analysis of sex differences.

In summary, this study examined effects of chronic khat use on psychophysiological and adrenocortical activity in a cross-sectional design and identified multiple alterations. The results demonstrate that khat users exhibited a more flattened diurnal pattern of adrenocortical activity, attenuated responses to acute stress, and reported greater negative affect than nonusers. Gender differences in cardiovascular responses to acute stress were attenuated among khat users, and khat users exhibited blunted cardiovascular responses to acute stress compared to nonusers. The extent to which these associations are due to effects of chronic khat use per se or instead reflect predisposing risk factors for khat use is yet to be determined. In light of the growing use of khat and the accumulated clinical observations demonstrating its harmful effects, the results are important in identifying mechanisms mediating long-term effects of chronic khat use on emotion regulation and risk for behavioral problems.

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FIGURE 1.

Mean positive affect (top figure), negative affect (middle figure), and physical symptoms (bottom figure) reported during the ambulatory assessment period. *Significant difference between khat users and nonusers ($p < .01$); **Significant changes across time in khat users but not in nonusers ($p < .05$).

FIGURE 2.

Mean positive affect (top figure), negative affect (middle figure), and physical symptoms (bottom figure) reported before and after performing the acute mental stressor during the laboratory session. *Significant difference between khat users and nonusers ($p < .01$); **Significant increases in response to stress in khat users but not in nonusers ($p < .05$).

FIGURE 3.

Mean cortisol concentration obtained during the ambulatory assessment period (top figure) and then before and after performing the acute mental stressor during the laboratory session (bottom figure). *Significant difference between khat users and nonusers ($p < .05$); **Khat users had higher cortisol levels than nonusers during early evening, but blunted cortisol levels in the morning ($p < .01$); ***Female nonusers had higher increases in cortisol levels from the evening to the morning compared to female khat users ($p < .05$).

FIGURE 4.

Mean systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), and rate pressure product (RPP) during baseline rest, during the acute mental stressor, and during rest recovery. The acute stressful challenge produced significant changes in all measures ($p < .01$). **Nonusers had higher diastolic BP levels than khat users during stress period ($p < .05$). #Higher heart rate in female nonusers compared with male nonusers ($p < .05$), but no such difference was found in khat users.

FIGURE 5.

Scatterplots depicting the relationship between salivary cortisol, negative affect, and physical symptoms after the acute stressors in khat users and nonusers. In nonusers, cortisol levels consistently correlated with negative affect and physical symptoms ($p < .05$). No such correlations were found in khat users.

TABLE 1.

Participant characteristics

	Khat users (<i>n</i> = 77)		Nonusers (<i>n</i> = 75)	
	Women (<i>n</i> = 14)	Men (<i>n</i> = 63)	Women (<i>n</i> = 44)	Men (<i>n</i> = 31)
Age (years) *	28.43 (1.49)	24.06 (.67)	21.32 (.63)	23.37 (.75)
BMI (kg/m ²)	24.58 (1.88)	20.68 (.44)	20.22 (.59)	20.84 (.82)
Education (years)	12.17 (1.19)	12.16 (.58)	11.39 (.72)	13.07 (.68)
Average sleep (hr/day) *	6.54 (.32)	6.85 (.29)	7.92 (.29)	7.20 (.18)

* $p < .01$, difference between khat users and nonusers.