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Effect of khat chewing on plasma levels of some hormones related to appetite regulation

Biochemistry

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ABSTRACT

Khat, a term used for the leaves and buds of the plant Catha edulis, is chewed as a cultural tradition in countries of East Africa and the Arabian Peninsula. Habitual khat use is associated with several adverse health effects. Among these effects suppression of appetite is one. Serum levels of some hormones related to appetite regulation were measured in habitual khat chewers. While insulin, c-peptide, T3, T4 and TSH were found to be within normal range, leptin and ghrelin levels were found to be significantly higher than controls. The observation of increased ghrelin levels is normal as the ghrelin level is associated with the fasting state. As the khat chewers have suppressed appetite, their empty stomach triggers the release of increased ghrelin. That, this increased ghrelin level does not cause hunger, may be due to the increased leptin level which keeps appetite suppressed. There seems to be a reversal of the normal reciprocal relationship between ghrelin and leptin levels and the appetite suppressing action of leptin predominates over the appetite stimulating action of ghrelin. Thus it appears that the antagonism to leptin effects by ghrelin may be deranged at the hypothalamus level in khat chewers. It appears that the active principles in khat may cause nervous and hormonal dysregulation of appetite.

INTRODUCTION:

Khat consists of whole fresh leaves and buds of the plant, Catha edulis (family Celastracea). Khat is chewed as a cultural tradition in East Africa and the Arabian Peninsula. Cathinone is khat's most psychoactive chemical which affects the nervous system "like a mild amphetamine" [1]. Cathine is a metabolic product of cathinone that possesses weak CNS stimulant properties [2].

There are reports in the literature of several health problems associated with khat abuse. Khat chewing is shown to cause gastrointestinal, dental and psychiatric problems. It is also associated with cancers including oral and head/neck cancers and liver, cardiovascular, urinary and ocular disorders. It is suspected to affect reproductive health leading to diminished sex performance [3].

Several nervous and hormonal factors regulate appetite, and therefore contribute to obesity and its opposite cachexia. The control center for hunger and satiety is the hypothalamus. Peripheral peptides and proteins directly interact with its neurons. These neurons produce peptides that stimulate food intake and weight gain. Among the major peptides produced by the hypothalamus are neuropeptide Y (NPY), agoutirelated peptide (AgRP), proopiomelanocortin (POMC) and cocaine- and amphetamine-regulated transcript (CART). The sensation of hunger and satiety is controlled by these neurons and peptides. Peripheral peptides leptin and insulin inhibit the synthesis and release of NPY while ghrelin and glucocorticoids stimulate it [4].

Circulating peptides also play important roles in appetitive behaviors. Ghrelin, produced mainly from stomach is an appetite stimulant. Ghrelin levels increase before meals and fall after food intake [5]. Thus ghrelin level is linked to food intake [6]. This action of ghrelin is due to stimulation of NPY and AgRP [7]. Ghrelin levels are low in obese subjects and high in thin subjects [8]. The gastrointestinal tract releases incretins in response to food ingestion. These hormones increase insulin secretion. Decreased gastric emptying is caused by the incretin, oxyntomodulin among its several effects [9]. Oxyntomodulin also suppresses ghrelin levels [10]. Insulin is another hormonal regulator of appetite. Insulin levels increase rapidly after a meal [11] and are appetite suppressing [12]. Leptin is another important appetite regulator. It is produced mainly by the white and brown adipose tissue. Leptin levels are related to body fat. The orexigenic peptides NPY and AgRP are inhibited by leptin in the hypothalamus while anorectic peptides POMC and CART are stimulated [13]. This causes decreased appetite. Obesity is caused in humans by the absence of leptin [14]. Hormones from the thyroid, T3 and T4 have been shown to increase appetite as well as energy metabolism [15, 16].

The appetite suppressant effects of chewing khat leaves have been reported earlier [17]. Appetite is affected by amphetamine-like substances by their action on the hypothalamus. Besides other effects, cathinone has been shown to delay gastric emptying [18]. Khat chewing decreases hunger and increases fullness, attributed to a prolonged gastric emptying [19]. As per some literature on metabolic hormones cathinone and amphetamine may share similarity in their effect on appetite related metabolism. In one study on the effect of khat chewing on appetite, decreased hunger and increased fullness was observed but ghrelin and PYY secretion was normal [19]. Leptin has been shown to mediate food restriction due to amphetamine [20].

In the present study blood levels of some appetite related hormones were determined in an attempt to understand the derangement of hormonal regulation of appetite in khat chewers,

MATERIALS AND METHODS:

50 habitual khat chewers were randomly selected for the study. Blood samples from the subjects were taken before and 4 hours after khat chewing. Assays of select hormones related to appetite regulation, namely leptin, ghrelin, insulin, c-peptide, T3, T4 and TSH were done using specific immunoassays. Reagent kits obtained from Human Diagnostics Ltd. were used and the kit provided protocols were followed for the immunoassays. Results were compared to available reference intervals for the hormones. Standard statistical analysis was performed to determine significance, correlation etc.

RESULTS & DISCUSSION:

All the values of hormonal levels before and after khat chewing are listed in Table 1. Figure 1 shows post-chewing values of all hormones as fold increase over respective pre-chewing values.

Table 1 Plasma levels of leptin, ghrelin, insulin, c-peptide, T3, fT4 and TSH in khat chewers before and 4 hrs after khat chewing.

	Khat chewers		
	Before chewing	4 hrs after chewing	p-value
Leptin (ng/mL)	3.2 ± 1.2	8.9 ± 3	<0.001
Ghrelin (pg/mL)	360 ± 220	720 ± 96	<0.001
Insulin (micIU/mL)	24 ± 12	61.1 ± 21	<0.001
c-peptide (ng/mL)	1.3 ± .5	2.4 ± 0.4	<0.001
T3 (ng/mL)	1.7 ± 0.5	1.6 ± 0.4	0.272
fT4 (ng/dL)	0.7 ± 0.3	0.8 ± 0.2	0.053
TSH (U/mL)	3.1 ± 0.6	3.2 ± 0.6	0.407

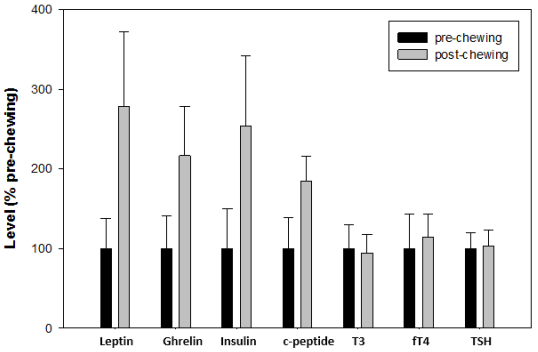

Figure 1. Hormone levels before and after chewing khat. Post-chewing values of each hormone is shown as percentage of pre-chewing value.

The results show that the thyroid hormone levels do not change significantly after khat chewing. Insulin and c-peptide levels are significantly increased ($p < 0.001$) after khat chewing which may be caused by the presence of glucose and other nutrients in khat. Levels of both ghrelin and leptin show marked increase ($p < 0.001$) after khat intake. Leptin is increased ~2.8 fold from 3.2±1.2 ng/mL to 8.9±3 ng/mL while ghrelin is raised 2 fold from 360±220 pg/mL to 720±96 pg/mL. The observation of increased ghrelin levels is normal as the ghrelin level is associated with the fasting state. As the khat chewers do not eat, their empty stomach triggers the release of increased ghrelin in an attempt to stimulate appetite. Ghrelin, produced mainly from stomach is an appetite stimulant. Ghrelin levels increase before meals and fall after food intake [5]. The action of ghrelin is due to stimulation of NPY and AgRP [7]. The orexigenic peptides NPY and AgRP are inhibited by leptin in the hypothalamus while anorectic peptides POMC and CART are stimulated [13]. This causes decreased appetite. Thus, normally a reciprocal relationship exists between ghrelin and leptin levels.

That, this increased ghrelin level does not cause hunger, may be due to the increased leptin level which keeps appetite suppressed. There seems to be a reversal of the normal reciprocal relationship between ghrelin and leptin levels and the appetite suppressing action of leptin predominates over the appetite stimulating action of ghrelin. Thus it appears that the antagonism to leptin effects by ghrelin may be deranged at the hypothalamus level in khat chewers.

The increase in ghrelin level may simply be attributed to empty stomach without any effect of khat. The significant ($P < 0.001$) increase in plasma leptin levels after chewing khat leaves may be attributed to the sympathometic action of cathinone [21] through the action of catecholamines [22]. Alternatively, persistent presence of acid in the stomach leads to gastrin and secretin release from the GIT [23], which consequently leads to an increase in circulating plasma leptin [24]. Cholecystokinin is released in large amounts [23] as a result of delayed intestinal absorption. The increase in cholecystokinin concentration results in a rapid and large increase in the concentration of leptin in plasma [25]. Moreover, cathinone, which enhances the release of catecholamines from nerve terminals [26], further increases gastrin concentration level [27], hence promoting leptin secretion. The increased leptin leads to weight loss through inhibition of intracellular lipid concentration by reducing fatty acids and triacylglycerol synthesis and concomitantly also increasing lipid oxidation [28]. Moreover, anorexia is caused by the increased leptin [29] and by the associated increase in energy expenditure [30]. Thus, increased plasma leptin may explain the decreased appetite observed in the majority of khat chewers [31].

CONCLUSION:

Blood levels of ghrelin and leptin were found to be significantly increased in habitual khat users 4 hours after khat consumption. Increased leptin levels may be the cause of suppressed appetite in khat chewers. A high level of ghrelin in the fasting state is unable to bring about the sense of hunger due to antagonism from increased leptin level. In the absence of any dysregulation in insulin and thyroid hormone secretion, the derangement of the reciprocal secretion of ghrelin/leptin may be the cause of suppressed appetite in habitual khat users.

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