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Khat use and appetite: An overview and comparison of amphetamine, khat and cathinone

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Abstract

Ethnopharmacological relevance—To understand the role of khat (*Catha edulis)* use on the aberrations in appetite and weight which are common comorbidities for khat and other amphetamine users.

Materials and methods—We provide a comprehensive overview and conceptual summary of the historical cultural use of khat as a natural stimulant and describe the similarities and differences between cathinone (the main psychoactive constituent of khat) and amphetamine highlighting the limited literature on the neurophysiology of appetite and subsequent weight effects of khat.

Results—Animal and some human studies indicate that khat produces appetite suppression, although little is known about mechanisms of this effect. Both direct and indirect effects of khat stem from multiple factors including behavioral, chemical and neurophysiological effects on appetite and metabolism. Classic and newly identified appetite hormones have not been explored sufficiently in the study of appetite and khat use. Unique methodological challenges and opportunities are encountered when examining effects of khat and cathinone including khat-specific medical comorbidities, unique route of administration, differential patterns of behavioral effects relative to amphetamines and the nascent state of our understanding of the neurobiology of this drug.

Conclusion—A considerable amount of work remains in the study of the appetite effects of khat chewing and outline a program of research that could inform our understanding of this natural amphetamine's appetite effects and help prepare health care workers for the unique health effects of this drug.

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Keywords

khat; cathinone; amphetamine; appetite; weight loss; health

1. Introduction

Khat is a natural amphetamine-like stimulant which comes from the leaves or young shoots of *Catha edulis*, a plant cultivated in East Africa and the Arabian Peninsula. Although synthetic amphetamine-class stimulants such as pure amphetamine (AMPH) have well known appetite suppression effects which may help account for, in part, the malnutrition and low body mass index seen with AMPH abuse (Ross et al., 2012), much less is known about their natural counterparts such as khat. This review seeks to describe khat's social/cultural history and argues that there is value in furthering research on its appetite suppression effect as a negative health outcome of khat use. Parallels between khat and the more extensively studied, and structurally similar, AMPH will be reviewed and used to propose new avenues for the study of the physiological mechanisms of khat's appetite suppression.

2. Khat as a cultural tradition and natural "amphetamine"

Khat has been widely consumed by residents in East Africa and the Arabian Peninsula for its psychoactive properties and associated social values. Chewing is the most common mode of administration, and fresh leaves are usually used during afternoon sessions that last two to five hours. Khat chewing has a social and cultural tradition, as it usually occurs while in company (Kennedy et al., 1983) and often runs along both family and social ties (Mahfouz et al., 2013). As with many psychoactive plants, khat continues to have a long history of indigenous traditional use, changes in use patterns due to immigration, and governmental attempts to control its use and trade (Anderson and Carrier, 2009; Gebissa, 2010; Sheikh, 2014). Indigenous use has been as persisted for eight centuries as a mild stimulant for enhanced energy during work, maintenance of prayers during long fasts, facilitation of social ties and as a commodity for trade, as dowry, and for dispute resolutions (Anderson and Carrier, 2009; Gebissa, 2010). Khat left to traditional use guided by culture is believed by users to be of little more harm than other stimulants such as coffee or tea but its future is unclear. Some have suggested that the future of khat could move towards either widespread legal commercialization or refinement into an illicit drug (Gebissa, 2010).

In many Middle East and East African cultures khat use motives differ by gender. Men use more frequently than women, though the use by women is increasing (Nakajima et al., 2013). Although both genders may refer to the upkeep of tradition to explain khat use, men reportedly use khat for occupational and recreational purposes while women's use is often for its perceived health benefits such as relief of headache, weight loss and assisting birth and delivery (Stevenson et al., 1996). Women tend to cite family as a source of motivation for *not* using khat (Nakajima and al'Absi, 2013). Concurrent tobacco use is quite high and also differs by gender. Two thirds or more of men use tobacco as well as khat, mostly in the form of cigarettes, but only one third of the women use tobacco via waterpipe (majority of use) or cigarettes (less than one quarter) (Nakajima et al., 2013). Despite clinical evidence to the contrary (al'absi et al., 2014; Bongard et al., 2011), users believe that khat decreases

depression (Wabe, 2011). Users also acknowledge negative effects of khat use such as insomnia and other sleep dysregulation, irritability and malaise during withdrawal (Gebissa, 2010; Nakajima et al., 2014; Stevenson et al., 1996).

Khat contains many different types of chemical constituents. Cathinone (CATH), the major alkaloid found in khat and a structural analog of AMPH, is responsible for most of khat's psychoactive properties (1975; Szendrei, 1980). Early work confirmed that tolerance can occur with khat (al'Absi et al., 2013; Nencini and Ahmed, 1989; Nencini et al., 1984; Schechter and McBurney, 1991) which is mediated, in part, through dopaminergic mechanisms (Schechter, 1990). There exists a rich body of literature documenting the subjective effects associated with acute khat use (Brenneisen et al., 1990; Halbach, 1972; Nencini et al., 1986; Pantelis et al., 1989), including euphoria, excited mood, increased wakefulness and alertness, and to most of our interest, suppression of appetite. In a recent study (Murray et al., 2008), khat's anorectic effect on humans was confirmed in a laboratory setting using a controlled experiment. In addition, rat studies using purified CATH have demonstrated that acute administration induces a significant reduction in food intake (Knoll, 1979; Zelger and Carlini, 1980). In a chronic experimental study, CATH was found to induce a marked reduction in body weight (Zelger and Carlini, 1980).

Although evidence from human and animal studies has confirmed khat's anorectic effect, limited information is known about its underlying mechanisms. Only one published paper examining the possible physiological mechanisms behind the anorectic effect of khat was found (Murray et al., 2008). Contrary to khat, the anorectic effect of AMPH has been studied extensively for decades. Given the similarities in the chemical structures and psychoactive properties between AMPH and khat's major constituent CATH, we will begin by examining the relevant knowledge on the anorectic effect of AMPH. From this, we will identify potential neurophysiological processes that might be responsible for the anorectic effect of CATH, and hence, khat. In the subsequent sections, we will then provide the conceptual basis for a potential program of research dedicated to the understanding of the mediators of the anorectic effects of khat use.

3. Brief review of neuroendocrine appetite modulators

The control of appetite and feeding occurs via highly interdependent peripheral and central signaling factors. These mediators can roughly be divided into appetite inducing (orexigenic) and suppressing (anorexigenic) factors, but it is important to note that there are complex interactions between factors which can blur this distinction. In general, there is much more that is known about appetite suppression than induction, due, perhaps, to the intense clinical and research interest in obesity. Among the appetite suppressing factors there are classic neurotransmitters and peptides (somatostatin, proopiomelanocortin (POMC), corticotropin-releasing hormone (CRH), peptide YY, serotonin (SE), cocaine- and amphetamine-related transcript (CART)), hormones (thyrotropin-releasing hormone (TRH), glucagon, amylin, glucagon-like peptide-1) and gut peptides (cholecystokinin (CCK), bombesin, enterostatin). At this time, a complete understanding of the complex signaling that initiates or terminates feeding is lacking despite significant progress over the past decade (Suzuki et al., 2012). As will be outlined in the subsequent sections, our

understanding of AMPH's effects on these central and peripheral appetite modulators is also rapidly developing but remains incomplete. Furthermore, translating what is known about AMPH to CATH is in its infancy.

4. Amphetamine and cathinone: Structural and neurophysiological similarities

Both AMPH and CATH are comprised of a linear chain of three carbons with a phenyl group attached to carbon #1 and an amino group attached carbon #2. The only structural difference between CATH and AMPH lies at the carbon #1 as it is oxidized to a ketone in CATH but not in AMPH (see Figure 1). Both AMPH and CATH contain two stereoisomers. It was originally reported that there exists only the S-(-)-cathinone in khat (1975; Szendrei, 1980) but a later report suggests a small amount of R-enantiomer is also present in khat (Dawson et al., 1994). Both AMPH and CATH are lipophilic and can readily cross the blood-brain barrier. However, the addition of a ketone makes CATH more polar (hence, less lipophilic) relative to AMPH. This difference manifests physiologically and behaviorally as CATH is found to be relatively weaker than AMPH in its interactions with the CNS to produce various behavioral symptoms (more details to follow). Nonetheless, the high degree of similarities in the structure and neurophysiological effects of CATH and AMPH have led some to refer to CATH as "khatamines" (Islam et al., 1990).

The stimulatory effects of AMPH and CATH are primarily mediated by their interactions with the catecholamine neurotransmitter systems, in particular, the dopaminergic (DA) and norepinephrinergic (NE) system after acute administration of AMPH (Heikkila et al., 1975; Von Voigtlander and Moore, 1973) and CATH (Cleary and Docherty, 2003; Kalix, 1982, 1983). Dopamine receptor antagonists or DA release inhibitors reverse or inhibit the behavioral stimulatory effects induced by AMPH (Davis et al., 1974; Lemberger et al., 1970) and CATH (Calcagnetti and Schechter, 1992; Kalix, 1986; Schechter, 1986).

The mechanisms behind CATH's effects on DA and NE systems have not been as extensively investigated, although they appear to be similar to those observed with amphetamines. Both cardiovascular and adrenocortical disruptions have been documented using human cross-sectional analysis, animal stress manipulation, and acute khat administration, all of which support both DA and NE mechanisms (al'Absi et al., 2013; al'absi et al., 2014; Nyongesa et al., 2013). Preliminary work indicates that CATH exhibits a high level of substrate activities on DA and NE transporters, albeit less potent than AMPH (Cleary and Docherty, 2003; Rothman et al., 2003; Simmler et al., 2013). This is consistent with the behavioral findings that CATH is less active than AMPH in inducing various behavioral effects in animals (Valterio and Kalix, 1982; Zelger et al., 1980) and appetite suppression (Zelger and Carlini, 1980). It has also been reported that AMPH and CATH interact with the serotonergic (SE) system. It is worth noting that certain structural modifications of synthetic AMPH can lead to increased SE activity (Rothman et al., 2001). Work on CATH has also demonstrated similar findings (Kalix, 1984; Nielsen, 1985; Rothman et al., 2003), suggesting that CATH's effect on increasing synaptic SE availability is present but very weak. In addition, there exist a large body of evidence suggesting that

activation of the SE system actually dampens the various stimulatory effects of AMPH and its analogs (Baumann et al., 2011; Breese et al., 1974; Hollister et al., 1976).

CATH's structural similarity to AMPH leads to functional similarities at both neurophysiological and behavioral level (see Figure 1 for a summary). Alterations in the NE and DA systems are believed to mediate the behavioral effects of the two compounds including appetite suppression. Numerous behavioral, neurophysiological and molecular studies have pointed to the NE and DA-dependent mechanisms in hypothalamus to be central to the anorectic effect of AMPH. Therefore, given the high structural and neurophysiological similarities between CATH and AMPH, it is reasonable to infer that the anorectic effect of CATH is most likely being mediated by the same mechanisms as identified in AMPH. In addition to CATH, cathine or *d*-norpseudoephedrine has been identified as an additional but minor psychoactive ingredient in khat with psychostimulant properties (Pehek and Schechter, 1990) but its appetite effects are unknown.

5. Anorectic effect of amphetamines & neurophysiological mechanisms

AMPH is no longer being used for the clinical management of obesity due to its high potential for abuse and addiction, but the neurophysiological mechanisms behind its anorectic effect are continuously being investigated. AMPH results in increased locomotion, decreased food consumption, and a negative energy balance (Walters et al., 2012) which has been linked to the lateral hypothalamus (LH) (Carlisle, 1964; Russek et al., 1973). Animal studies support the notation that LH-innervating NE and DA fiber systems but not SE fibers are involved in the anorectic effect of AMPH (Ahlskog, 1974; Carey, 1976; Carey and Goodall, 1975; Carlisle and Reynolds, 1961; Samanin et al., 1975). Pharmacological studies using NE and DA synthesis inhibitors (Leibowitz, 1975), NE receptor antagonists (Leibowitz, 1975; Leibowitz and Rossakis, 1978; Sanghvi et al., 1975), and DA receptor antagonists (Chen et al., 2001; Leibowitz, 1975) all showed attenuation or complete blockage of AMPH's anorexic effects. Combining these pieces of evidence with the knowledge that AMPH increases the synaptic availabilities of NE and DA, it is suggested that NE and DA dependent mechanisms in the LH most likely mediate the anorectic effect of AMPH.

In summary, it is clear that AMPH suppresses appetite by increasing the synaptic availabilities of NE and DA in hypothalamus, and subsequently activates the NE- and DA-dependent mechanisms that attenuate the central nervous system control of food intake. In addition to the catecholamine effects, recent studies have reported that the interaction between hypothalamic DA and neuropeptide Y (NPY), an orexigenic neuropeptide, plays a key role in the anorectic effect of AMPH. Molecular evidence showed that AMPH treatment to hypothalamic NPY neurons reduces the expression of NPY at both transcriptional and posttranslational levels (Hsieh et al., 2006; Hsieh et al., 2005). However, it is likely that NPY is not the sole mediator of these effects. Other central appetite messengers such as proopiomelanocortin (POMC), cocaine and amphetamine regulated transcript (CART), and orexin, as well as peripheral appetite messengers such as leptin, ghrelin and glucose, might also be involved. Many of these factors are sensitive to catecholamine signaling in the paraventricular, arcuate nucleus, ventromedial hypothalamus and suprachiasmic nucleus

neurons containing Agouti gene-related protein (AgRP) and CART receptors. Table 2 demonstrates the extensive breadth and sophistication of the current work on the appetite effects of AMPH on a wide variety of appetite modulators. Selected references from this broad body of work span both human and animal observational and experimental studies utilizing behavioral, physiological, neurophysiological, microbiological and genetic techniques. As will be argued in subsequent sections, our understanding of CATH's appetite suppression is relatively less sophisticated but warrants further investigation.

6. Anorectic effects of khat

Early in the experimental investigation of CATH it was suggested that CATH's inhibition of food intake was greater than equivalent AMPH doses (Knoll, 1979), though others have challenged this (Zelger and Carlini, 1980). In addition to catecholamines, other metabolic hormones that are responsive to AMPH are also responsive to CATH. Both triiodothyronine and thyroxine are elevated in a similar manner by high doses of AMPH and CATH, though CATH appears to elevate thyroxine earlier than AMPH (Islam et al., 1990). This limited literature on metabolic hormones supports the hypothesis that CATH and AMPH may have similar effects on both direct and indirect appetite modulators and metabolism.

As indicated above, several gut peptides are important appetite modulators. These include orexigenic factors such as orexin and ghrelin and the anorexigenic factors such as leptin, peptide YY (PYY), bombesin and glucagon-like peptide-1 (GLP-1). In one of the few studies of appetite hormones, khat chewing, at least by habitual users, decreased subjective feelings of hunger and increased subjective feelings of fullness despite no change in ghrelin or PYY secretion (Murray et al., 2008). This is in contrast to AMPH where leptin has been called into question as a mediator of food restriction sensitization of d-amphetamine's reward effects (Hao et al., 2006). Whether other critical distinctions exist between appetite hormones and the effects of AMPH and CATH remains to be seen.

7. Health and behavioral properties of khat, CATH & AMPH

The previous discussion outlined early evidence of khat's resemblance to AMPH in basic structure, neurophysiology and appetite effects. It may also be instructive to consider the ways in which khat is subtly distinct from AMPH, particularly in relation to diseases or conditions that could indirectly affect appetite or feeding behaviors. Mounting evidence indicates that chronic khat use can result in unique health effects less frequently seen in AMPH users. These health effects may indirectly impact appetite through the presence of sickness behavior, oral cavity lesions or changes in macronutrient selection. Any study of appetite in experimental animals or khat using human samples will need to consider these secondary effects in the design of experimental or quasi-experimental studies. Each of these will be discussed in turn with the purpose of identifying additional avenues of research in a program of study specific to the appetite effects of khat.

7.1. Health effects as secondary factors

The impact of hepatotoxicity and renal dysfunction on appetite and weight could potentially be quite important to the study of the anorectic effect of CATH. Sickness behaviors such as

fatigue, nausea and changes in both appetite and thirst are common symptoms of liver and kidney disease (Strid et al., 2002). Experimental evidence in Sprague-Dawley rats indicates that minor use of khat (subchronic) can lead to impaired liver and kidney functioning (Alsalahi et al., 2012). Changes in weight and leptin levels were seen after 4 weeks of use in male but not female rats but impaired renal function was evident in female but not male rats in response to subchronic use (Alsalahi et al., 2012). Hepatotoxicity in this study was evident in both male and female rats. A case report of similar hepatotoxicity (acute hepatitis) in a human khat user has been published which was interpreted by that author to be more similar to amphetamine derivatives with a higher SE profile such as 3, 4-methylenedioxy-N-methylamphetamine (MDMA) (Chapman et al., 2010). MDMA has long been linked to serotonergic toxicity and dehydration, which may be important secondary appetite modulating effects (Parrott, 2001). Renal dysfunction has also been documented with other drugs such as heroin, cocaine and polysubstance abuse (Milroy and Parai, 2011) but relatively less often with AMPH abuse. Chronic kidney disease has also been linked to changes in ghrelin, leptin and cytokines leading to decreased appetite, weight loss and muscle wasting (Gunta and Mak, 2013; Suzuki et al., 2013). Thus, any study of these appetite regulators in human khat users should consider verifying adequate hepatic and renal functioning. Some investigators have noted that such renal and hepatic health effects are found in immigrants but not khat users living in the regions where the khat is grown, possibly due to suspected contamination at export (Coton et al., 2011; Douglas et al., 2011).

Khat-induced changes in activity levels, feeding and macronutrient selection due to the nature of drug delivery (chewing large boluses of fresh leaves) may also indirectly affect appetite. Cathinone's similarity to AMPH has been proposed as a justification for similar effects on appetite and weight, it is important to note that not all investigators find a negative correlation with khat use and BMI. For example, Yemeni medical students were shown to demonstrate a positive correlation with khat use and BMI, possibly due to a relative sedentary lifestyle related to khat use (Laswar and Darwish, 2009). Others have noted that khat's bitter flavor leads users to excessively consume sweets (candy, sugar cubes, etc.) to counteract the taste which, in turn, elevates blood sugar, weight and risk of dental caries (Douglas et al., 2011). Taken together these factors may be a behavioral source of increased diabetes risk seen in some khat users (Hassan et al., 2007).

Finally, khat may indirectly affect appetite and feeding behavior through oral cavity lesions. A population survey of 1,500 immigrant showed that khat users demonstrated increased abnormal oral pigmentation, tooth staining, xerostomia (dry mouth) and risk of dental caries compared with nonusers (Yarom et al., 2010). Khat users who immigrated to the United Kingdom showed a 14% higher rate of symptomatic dental and medical service use (Kassim and Croucher, 2012). Xerostoma and increased cavities have not been documented with the more pure and traditional AMPHs (*d*-amphetamine, *l*-amphetamine), but synthetic drugs such as methamphetamine are well known to result in high rate of caries, xerostomia and excessive tooth wear (Hamamoto and Rhodus, 2009; Ravenel et al., 2012). Although polysubstance abuse limits the ability of dental researchers to *directly* implicate methamphetamine in the presentation of "meth mouth" (Leserman Robbins et al., 2012), the effects of excessive cavities, xerostomia and tooth loss common with khat use strongly

suggests an indirect effect on feeding behavior and nutrient content (e.g. increased sweet consumption to counteract xerostomia) due to the use of some, but not all, AMPH-based substances. Likewise, increased sweet consumption may lead to subsequent dental caries (Douglas et al., 2011) despite the fact that khat use in humans may shift the bacterial profile of the mouth towards beneficial species (Al-Hebshi and Skaug, 2005; Yarom et al., 2010).

7.2. Motor and thermoregulation effects as secondary factors

In addition to changes in diet, khat's effects on motor behavior have been likened to those of AMPH (Kalix, 1980). A direct comparison of khat to AMPHs using catecholamine antagonists supports that the motor patterns demonstrated in experimental animals treated with CATH is likely secondary to dopaminergic and serotonergic effects (Connor et al., 2002). In this study, motor patterns were more circumspect at lower khat doses (head twitch) and at higher khat doses (stereotypies) than AMPH which had a broader range of spontaneous gross motor behaviors. Although still a limited literature, this suggests that a simultaneous comparison of motor effects induced by CATH and AMPH as a behavioral mechanism to weight loss will be important.

Understanding the appetite and weight effects of AMPH-class stimulants, either natural or synthetic, also requires an examination of thermoregulation as well as behavioral neuromodulation. Hyperthermia is a major adverse side effect of acute use of several AMPH-class stimulants and may be one mechanism behind the weight loss associated with AMPH (Parrott, 2001). It has been known for some time that both AMPH and CATH increase brown adipose tissue and rectal temperature in rats, though AMPH shows a threefold higher temperature response than CATH (Tariq et al., 1989). Acute administration of a high dose of CATH (10 mg kg^{-1}) resulted in elevations to rectal temperature but not tail temperature in rats while MDMA decreased temperature at all doses and time points (Shortall et al., 2013). This work also indicated that housing (single versus three per cage) also had a significant modulating effect on thermogenic and catecholaminergic changes. How this finding relates to the highly social nature of human khat and other AMPH-class stimulant use is not clear.

8. Conclusions and future directions

The above review highlights the chemical, neurophysiological, health and behavioral similarities and differences between AMPH and CATH. These similarities have prompted some to coin the term "khatamines" to reflect the broad range of similarities between khat's CATH and AMPH. Both khat and AMPH have been linked to appetite changes and weight loss. As discussed above, numerous studies of critical neuroendocrine appetite modulators have been conducted related to AMPH, however, to our knowledge, many of these modulators such as NPY, CART and POMC have not been studied specific to khat (natural) or pure CATH. POMC's role in the analgesic effect of khat (Nencini et al., 1986) has been investigated but not for its possible role in khat's anorectic effect.

Given the extensive and meaningful similarities between these molecules, further research is needed. While advances in molecular biology, neuroimaging and chemistry will undoubtedly be invaluable to the further study of appetite and chronic khat use, advancing

the psychometric validation of behavioral and psychological tools in the native language of local users will be important (Nakajima et al., 2012; Nakajima et al., 2014). In addition, a great deal of research is needed such as direct comparisons of CATH to multiple types of AMPH compound's cellular and molecular neurophysiology, studies of health-related effects on feeding behavior, analyses of thermogenesis, observation of drug-induced motor behavior changes in both animal and human subjects, study of gender differences in drug response at all levels of analysis (molecular to whole animal), and toxicological studies of the purity of natural khat. A program of study on the direct and indirect effects of khat on feeding behavior would include studies of human and experimental animals that consider the potential indirect effects of plant bitterness-induced behavioral changes on macronutrient selection. In such a program of research, the potential for sickness behaviors such as malaise, nausea and appetite loss induced by sub-clinical hepatic and renal abnormalities in khat chewers are also important considerations in need of controlled experimental or quasi-experimental studies. Studies of the effects of khat on gut associated neuromodulators such as NPY, leptin, and ghrelin are also needed. We have shown that chronic tobacco use, which is common to khat chewers, disrupts leptin, that PYY and leptin correlate with nicotine craving, and that leptin and ghrelin predict relapse with attempted smoking cessation (al'Absi et al., 2011; al'Absi et al., 2014; Potretzke et al., 2014). Although khat use is associated with heightened leptin levels (Al-Dubai et al., 2006), the same breadth and sophistication in understanding khat or CATH's appetite regulation is lacking. Additionally, research is needed examining the purity of the khat product due to contaminants at export when considering behavioral, chemical, and neurophysiological effects on appetite and metabolism. The relatively less severe withdrawal symptoms of khat (Thomas and Williams, 2013) may also affect free feeding behavior in the positive direction (potentially less prolonged anorexia), which may account for the inconsistent correlations between khat use and BMI.

This review suggests that the neuroendocrine evaluation of khat's anorectic effects should start with several hypotheses. One hypothesis is that CATH's anorectic effect is secondary to NE and DA-dependent mechanisms within the hypothalamus. It is possible that, as with AMPH, the anorectic effect of CATH is mediated by NPY and requires co-stimulation of both D1 and D2 receptors. Further, pharmacologic studies of the impact of the additional ketone in CATH may be critical to understanding CATH's seemingly weaker appetite suppressant effect. It can also be hypothesized that cathine and d-norpseudoephedrine independently or in combination may contribute to different facets of the appetite suppressant effect of khat and clarifying their pharmacological effect on all direct and indirect feeding behaviors could be fruitful. It is important to not lose sight of the weak, but significant, SE effect of CATH.

All of these hypotheses remain hypothetical until confirmed by a thoughtful, systematic program of research. Drug use on an international scale causes a critical drain on national economies. While khat is currently a relatively smaller proportion of substance abuse in Europe and the U.S., it is gaining increased political attention (Odenwald et al., 2010). It is primarily consumed in localized East African and Middle Eastern immigrant communities across the U.S. and Europe. Although initially it was thought to be a substance that was only used by adult immigrants with experience with khat in their home country (Klein, 2012),

anecdotal evidence suggests that khat is used by both first generation immigrants and UK born young adults for its unique, “mellow” high and presumed safety (Holligen, 2009). It is possible that the same factors leading to its adoption by new users in the UK could also hold true in the U.S. A careful program of research to understand critical health consequences such as appetite changes and weight loss from the use of khat is warranted.

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Glossary

AgRP	Aguoti gene-related peptide
AMPH	Amphetamine
BMI	Body mass index
CART	Cocaine- and amphetamine-related transcript
CATH	Cathinone
CCK	Cholecystokinin
CRH	Corticotropin-Releasing Hormone
DA	Dopamine
GLP-1	Glucagon-like peptide 1
LH	Lateral hypothalamus
MDMA	3,4-methylenedioxy-N-methylamphetamine
NE	Norepinephrine
NPY	Neuropeptide Y
POMC	Proopiomelanocortin
PYY	Peptide YY
SE	Serotonin
TRH	Thyrotropin-releasing hormone

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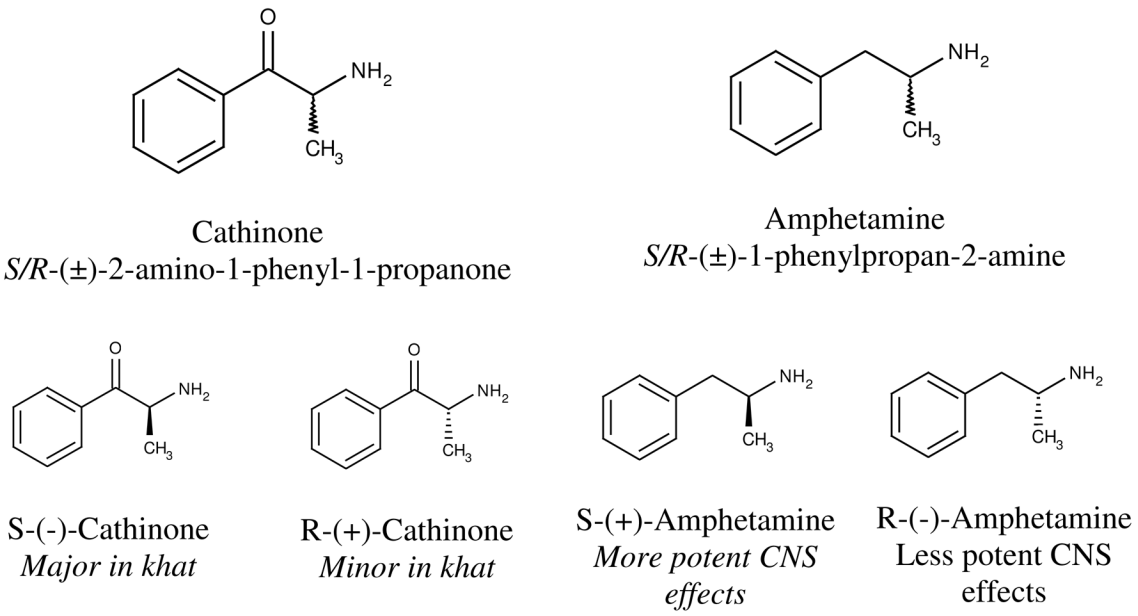

Figure 1.
Cathinone, amphetamine, and their stereoisomers

Table 1

A comparison of the physical, behavioral, and neurophysiological properties of amphetamine and cathinone.

		Amphetamine	Cathinone
Chemical		A linear chain of three carbons A phenyl group attached to carbon #1 An amino group attached to carbon #2. Lipophilic Readily cross the blood-brain barrier Pulse rate and blood pressure increase	Same, except Carbon #1 is oxidized to a ketone (see Figure 1) May delay gut motility
Behavioral	Human	Euphoria Excited mood Increased wakefulness Increased alertness Reduction of appetite Decrease response inhibition Toxic psychosis	Mostly the same, but less potent Increase response inhibition
	Animal	Increased spontaneous locomotion Stereotypical behaviors Reduction of food intake	Similar, but more circumspect
Neurophysiology	DA	Increase synaptic DA availability, via Transporter-mediated reuptake inhibition and DA release	Same, but less potent
	NE	Increase synaptic NE availability, via Transporter-mediated reuptake inhibition and NE release	Same, but less potent
	SE	Minimal interaction	Same

Table 2

A comparison between amphetamines and cathinone on known neuroendocrine appetite modulating factors.

	Amphetamines	Khat/Cathinone
Appetite Inducing		
Neuropeptide Y (NPY)	AE[1–4]	--
Norepinephrine	AE[5–9]	AE[10,11]
Aguoti related peptide (AgRP)	--	--
Orexin A & B	AE-NA[12–14]	--
Melanin concentrating hormone (MCH)	--	--
Ghrelin	AE-NA[15,16]	HE[17]
Appetite Suppressing		
Proopiomelanocortin (POMC)	AE[18,19]	--
Cocaine and amphetamine regulated transcript (CART)	AE[20,21]	--
Leptin	AE-NA[22]	AE[23] HE[24]
Thyrotropin releasing hormone (TRH)	AE[25,26]	--
Melanin	AE-NA[27]	--
Corticotrophin releasing hormone (CRH)	AE-NA[27]	--
Bombesin	AE[28]	--
Glucagon	AE-NA[29]	--
Glucagon-like peptide-1 (GLP-1)	AE-NA[30]	--
Peptide YY (PYY)	AE[28]	HE[17]
Apolipoprotein A-IV	--	--
Amylin	--	--
Somatostatin	AE-NA[31]	--
Enterostatin	--	--
Ciliary neurotrophic factor (CNF)	--	--
Serotonin	AE[32–35] HE[38] HO[39]	AE[36,37]

NOTE: Abbreviations include AE = Animal Experimental, AE-NA = Animal Experimental Not Appetite specific, HE = Human Experimental, HO = Human observational studies. Select references are shown but are not meant to be comprehensive.

[1–4] Gillard et al., 1993; Hsieh et al., 2006; Hsieh et al., 2005; Kuo et al., 2012;

[5–9] Cleary and Docherty, 2003; Harris and Baldessarini, 1973; Heikkila et al., 1975; Holmes and Rutledge, 1976; Kalix, 1983;

[10,11] Cleary and Docherty, 2003; Kalix, 1983;

[12–14] Estabrooke et al., 2001; Fadel and Deutch, 2002; McPherson et al., 2007;

[15,16] Suchankova et al., 2013; Wellman et al., 2013;

17 Murray et al., 2008;

18,19 Jaworska et al., 1994; Kuo et al., 2012;

20,21 Rogge et al., 2008; Vicentic and Jones, 2007;

22 Hao et al., 2004;

23 Mahmood and Lindequist, 2008;

24 Al-Dubai et al., 2006;

25,26 Manberg et al., 1979; Volkoff, 2013;

27 Smith et al., 2008;

28 Morley and Flood, 1987;

29 Morawska et al., 1998;

30 Egecioglu et al., 2013;

31 Tatsuoka et al., 1987;

32–35 Bendotti et al., 1982; Heal et al., 1998; Rech et al., 1984; Sanghvi et al., 1975;

36,37 Kalix, 1984, 1986;

38 Silverstone et al., 1992;

39 Bray, 1993