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Review

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.

Contents

Abbreviations: 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

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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 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 (Bongard et al., 2011; al'Absi et al., 2014a, 2014b), 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 (Stevenson et al., 1996; Gebissa, 2010; Nakajima et al., 2014).

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 (United Nations, 1975; Szendrei, 1980). Early work confirmed that tolerance can occur with khat (Nencini et al., 1984; Nencini and Ahmed, 1989; Schechter and McBurney, 1991; al'Absi et al., 2013) 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 (Halbach, 1972; Nencini et al., 1986; Pantelis et al., 1989; Brenneisen et al., 1990), 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