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Does khat chewing increases the risk of *Mycobacterium tuberculosis* infection by macrophage immune modulation?

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ABSTRACT

Drug abuse is a serious problem associated with different pathological outcomes including modulating the immune system. Drug abuse is rising in Saudi Arabia and so as TB, a disease of worldwide significance, caused by immunological modulation in the host system. Khat chewing is a common practice in Arabian Peninsula which is now gaining momentum in other parts of the world. It is considered as an addiction. It has been associated with different adverse outcomes such as periodontitis, oral leukoplakia and oral cancer and also has shown to promote apoptotic cell death through cysteine proteases. The active ingredient of khat, cathinone is shown to have immunomodulatory effect. In principle, this leads to enhanced susceptibility to various infections. The present study is designed to delineate the mechanism of immunomodulation produced by khat/cathinone in human/mouse macrophage. Further, this activity will be evaluated both in vivo and in vitro in response to infection with *Mycobacterium smegmatis* to get an insight if there exists a co relation between the *Mycobacterium tuberculosis* infection and khat chewing.

Introduction

Drug abuse is a serious problem of global significance, with alarmingly increasing incidence [1]. In addition to socioeconomic problem, it has been associated with untoward health problem including modulating the immune system [2]. This modulation sometimes takes the form of immune suppression leading to an enhanced susceptibility to various infections among drug abuser [3,4].

Khat¸ a green leaved plant is widely used for its stimulatory and euphorgenic effects in Saudi Arabia and Eastern Africa [5]. However, incidence of khat chewing is also increasing in Europe and North America due to global migration [6].

Fresh leaves and shoots of the plant contain an alkaloid cathinone or cathine which is the main psychoactive ingredient [7]. When the leaves and shoots are chewed, cathinone is extracted in saliva and gets actively absorbed in the blood to elicit its adverse effect on various organs including central nervous systems [8,9]. Apart from these, studies demonstrated khat chewing as a risk factor for the development of oral cancer [5]. The organic extract of khat has also been shown to induce apoptosis through the activation of caspases [10–12].

Interestingly cathinone or cathine shares structural and functional similarity with amphetamine which has been shown to have immunomodulatory effects on macrophages [13]. To this end, studies carried out in tandem along with synthetic amphetamines demonstrated the role of cathinone in suppressing the production of IL-2, B-cell proliferation and cytotoxic T lymphocytes [2]. Thereby representing a formidable challenge to the immune system.

Given to immunomodulatory/immunosuppressive effect of addictive compounds it is imperative to look closely at their functions, particularly with regards to the diseases which are associated with immunomodulation or immune suppression. Among such diseases is "tuberculosis", spread by inhalation of droplet nuclei containing the tuberculosis bacilli. According to 2011 WHO report it is a major cause of morbidity and mortality accounting almost 8.8 million incidence among which 0.35 million deaths are associated with co infection with HIV [14].

Chronic pulmonary infection occurs through phagocytosis, bacterium evade the host immune response and create a favorable niche for their survival, replication and subsequent infection. It is suggested that pro/anti inflammatory cytokine balance contribute significantly for long term sequelae and their associated pathogenesis [15]. Interferon (IFN)-γ and IL-2 produced by T lymphocyte is a key determinant in the control of *Mycobacterium tuberculosis*

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infection. In addition Mycobacterium significantly induces the secretion of tumor necrosis factor alpha (TNF-α) by macrophages, dendritic cells and T cells, and is required for the control of *M. tuberculosis* infection especially when it is in its active stage [16]. All of the above mentioned cytokines are key players who share, a cross talk with active chemical of common addictive substances, in this case cathinone.

Hypothesis

Given to the structural similarities between cathinone and amphetamine we hypothesized that khat-chewing (and ultimately its active ingredient cathinone) possibly shares a cross talk with host immune response by suppressing it thereby favoring the *M. tuberculosis* infection.

First question: what do we already know about the subject?

It is well known that certain addictive compound alter the immune response. Studies carried out till date shows differential modulation of immune function by various addictive compounds especially for amphetamines, morphine or opiates related drug [2,19]. This activity may be either suppressive or stimulatory depending upon the nature of the target cells and the conditions of exposure. For example, in vitro Heroin has been extensively related with immune suppression and enhanced susceptibility to infection [4]. Since khat has been described as a natural amphetamine it would be interesting to investigate whether it elicits similar effect especially in response to infection.

Second question: what does our proposed theory add to the current knowledge available and what benefits does it have?

Our proposed hypothesis is likely to provide more holistic approach to address macrophage immune modulation associated with aggressive khat chewing. This will also help explore the pro/anti-inflammatory effect of cathinone in macrophages infected with *Mycobacterium smegmatis*.

Currently available knowledge discusses more about the psycho stimulatory effect of khat. This study will juxtaposed khat chewing with more serious ill effects related to opportunistic infectious diseases such as tuberculosis. This will ultimately add potential weightage to different anti-khat chewing campaigns by government institutes to bring mass awareness in the region.

Third question: among numerous available studies, what special further study is proposed for testing the idea?

This idea can be tested in further prospective studies involving large cohort of khat chewing patients suffering from different infectious diseases.

Evaluation of hypothesis

The increased incidence of tuberculosis in Kingdom of Saudi Arabia over the last decade call for delineation of host factors that control susceptibility to tuberculosis. To this end, study can be performed among the khat chewers affected with tuberculosis and those not affected with tuberculosis. Secondly, the same can be validated in vitro using cathinone, an active compound of khat along with non pathogenic tuberculosis bacilli, *M. smegmatis* in the presence and absence of test compounds to delineate their function. The panel of immune function assays can be carefully selected to represent host immune response.

Lastly, in vitro experimental results can be fully evaluated by in vivo exposure of drug in CBA mice [17] this will help argue some very important questions related to drug metabolism and its associated immunomodulatory activity in a holistic manner, if any.

Suggested limitations of hypothesis

The immune modulation may also be triggered by some other unknown mechanism such as autoimmunity, or latent unknown infection. Carrier state may also bias the hypothesis. So the subjects having diabetes, pregnancy, inflammatory bowel disease, multiple sclerosis, etc. need to be excluded from the study.

Discussion

Khat chewing is one of the most common socially accepted substance abuse in Arabian Peninsula. Although there are now discussions emerging whether it should be branded as drug abuse or not, considerable amount of data suggested its adverse effects on social well being, financial losses and susceptibility to certain diseases.

Interestingly, the active ingredient cathinone which shares structural homology with amphetamine has been not scrutinized for its immunomodulatory role in infectious diseases. In recent years tuberculosis is on rise in Saudi Arabia, several factors have been observed to influence the rate of infection; there are more than six million expatriate from different endemic regions and more than three million pilgrims visiting the holy cities [18]. One of the interesting aspect would be to look into the fact that khat is chewed on regular basis in different regions of Saudi Arabia especially in southeastern province does this correlate with the rise of these incidences? Given to the fact that more or less, common denominators for the spread of infection are same in Saudi population such as hygiene, overall nutrition, etc.

Conclusion

Understanding the effect of khat chewing in modulating the immune response will help bring awareness about the adverse effect of khat chewing among the population. Also the study will help understand the role of khat or its active compound in infectious diseases.

Conflict of interest

All the authors declare that there is no conflict of interest.

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