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ARECA NUT SYMPOSIUM

Neurological aspects of areca and betel chewing

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Abstract

Betel quid chewing has been claimed to produce a sense of well-being, euphoria, warm sensation of the body, sweating, salivation, palpitation, heightened alertness and increased capacity to work. These effects suggest that betel quid chewing affects predominantly the central and autonomic nervous systems. Several studies have been conducted to elucidate the central and autonomic effects of betel quid chewing. The results are: (1) betel quid chewing increased the heart rate with onset within 2 minutes, maximal effect within 4–6 minutes and an average duration of 16.8 minutes. The cardio-acceleratory response was more prominent for fresh and occasional chewers than for habitual chewers; (2) betel quid chewing increased the skin temperature with onset and duration similar to a cardio-acceleratory response. The hyperthermic effect was abolished by atropine and partly inhibited by propranolol. (3) Betel quid chewing had no effect on simple reaction time but shortened the choice reaction time. (4) Betel quid chewing produced widespread cortical desynchronization of EEG. (5) Chewing of one or two betel quids attenuated the sympathetic skin response while continued consumption of more than two betel quids affected the RR interval variation. (6) Plasma concentrations of noradrenaline and adrenaline were elevated during betel quid chewing. These studies have confirmed several effects claimed by betel quid users. The effects of betel quid chewing appeared to be habit-related and dose-dependent. Although arecoline has been thought to be responsible for several effects of betel quid chewing, the present data suggest a role also played by sympathetic activation.

Introduction

The use of betel nut masticatory has been widespread in Southeast Asia and the South Pacific islands, and highly valued for its psychoactive properties in reducing tension, producing euphoria or a sense of well-being, increasing the capacity to work and providing the means of social interactions and rituals.[1,2]

The claimed effects of betel quid chewing are euphoria, a sense of well-being, palpitation, salivation, diaphoresis, heightened alertness, warm sensation of the body, combat against hunger and increased stamina.[1–3] Arecoline, the major alkaloid of the areca nut, has been thought to be responsible for several of the claimed effects.[4–6] Arecoline is one of the naturally occurring alkaloids, with parasympathomimetic properties acting on both muscarinic and nicotinic receptors.[5,6] Arecoline induces an arousal response in animals and a cardio-acceleratory response in humans.[7–11] However, there are other alkaloids in areca nut, i.e. arecaidine and guvacine, which are GABA uptake inhibitors.[12,13] Phenolic compounds in the piper betle flower or

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leaf are stimulators to release catecholamines from chromaffin cells *in vitro*.[14]

Despite some regional variations, betel quid preparations consist of the nut of the palm tree *Areca catechu*, quicklime and some type of psychoactive leaf of the plants.[1–3] Undoubtedly, chewing of betel quid causes different reactions and interactions before those active compounds are absorbed into the circulation.[15] Arecoline in the presence of lime is converted into arecaidine, which lacks typical parasympathetic properties, and the amount of arecoline entering the circulation may not be sufficient to exert cholinergic and other actions. Therefore, interpretation of experimental data are difficult unless these data are obtained from humans and active compounds in the blood or the brain are determined. Despite the antiquity and popularity of betel chewing, its claimed effects have not been investigated systematically in humans. This paper will address the psychoneurological aspects of betel quid chewing from our human studies, and hopefully warrants further research.

Neurological aspects of betel chewing

The following studies were carried in normal healthy subjects. The betel quid used was the most popular one in Taiwan, which consists of fresh nut of *A. catechu* (areca nut), piper betle flower and slacked lime paste, which contains a Chinese herb (*Acacia catechu*) to promote the flavour. Controls were usually those who chewed areca nut only and those who chewed fruit-flavoured chewing gum. Study subjects were habitual users, but in some studies might include fresh chewers and occasional chewers.

Cardiovascular response

All three groups of habitual, occasional and fresh chewers showed an increase in heart rate following betel quid chewing.[16] The onset was within 2 minutes after chewing, peak effect was reached within 4–6 minutes and the effect lasted for an average of 16.8 minutes. The mean increase in heart rate was 13.3 beats/min for habitual users, 16.2 beats/min for occasional users, and 17.0 beats/min for fresh users, suggesting tolerance or habituation for chronic users. On the other hand, blood pressure was significantly elevated only for the fresh chewers.

Heightened alertness

To investigate the claims that betel quid chewing increases alertness and improves motor responses, simple and choice reaction times (SRT and CRT) were studied in habitual users.[17] Control consisted of chewing gum and practice groups. In the SRT task, reaction times were not different among the three groups. In the CRT task, the betel quid and chewing gum groups showed a significant shortening of reaction time, but the betel quid group had a higher degree of statistical significance ($p < 0.0001$ vs. $p = 0.0379$). The data suggest that shortening of CRT from betel quid chewing is probably due partly to chewing itself and partly to a cholinergic arousal mechanism.

EEG activity of 52 betel quid users was studied by spectral analysis and topographic mapping before and during betel quid chewing.[18] Betel quid chewing increased both alpha and beta activities but decreased theta activity. These effects were most prominent for beta rhythms. Topographic mapping revealed that altered rhythms were restricted to the occipital areas for alpha and widespread for both beta and theta. The data suggest that betel quid chewing causes EEG changes associated with a state of arousal and, to a lesser degree, a state of relaxation.

Body temperature effect

Because betel quid chewing produces sweating, facial flush and a warm sensation of the body, skin temperature was recorded before and during betel quid chewing in habitual chewers.[19] Betel quid chewing caused an increase in skin temperature from 0.5 to 2.0°C, and this hyperthermic response was abolished by atropine and partially inhibited by propranolol. The data suggest that both parasympathetic and sympathetic mechanisms are involved in the skin thermal response to betel chewing.

In a preliminary study using carotid Doppler to measure blood flow of the carotid system plus measurements of blood pressure and heart rate in habitual, occasional and fresh chewers, blood flow was significantly increased during betel quid chewing only in the external and common carotid arteries. This flow increase was associated with facial flush sensation. Heart rate was prominently increased, especially in fresh and occasional chewers, and associated with palpitation.

Autonomic functions

To investigate further the involvement of the autonomic nervous system on the effects of betel chewing, two autonomic function tests were studied before and during betel quid chewing.[20,21] One was the sympathetic skin response (SSR) which is a psychophysical response mediated by the central and peripheral sympathetic pathways.[22] Another was the RR interval variation (RRIV) which depends partly on the parasympathetic reflex mediated by the vagus nerve.[22]

SSR was recorded from the hand by stimulation of the contralateral median nerve at the wrist.[20] While the response latency remained unchanged, the response amplitude showed a progressive reduction during chewing and a gradual recovery after chewing. The altered response was similar to that seen in palmar hyperhidrosis,[23] suggesting the activation of sympathetic pathways.

In the RRIV test, when one or two betel quids were consumed, the main effect was a cardio-acceleratory response.[21] With increasing consumption of betel quids, there was a reduction in RRIV, particularly during deep breathing. Consumption of betel nut only or chewing gum had no effects on RRIV. The dose-dependent responses suggest that usual consumption of one or two betel quids cause mainly a sympathetic activation while heavy consumption will affect parasympathetic function.

Sympathoadrenal response

To investigate further the sympathetic involvement in the effect of betel quid chewing, plasma concentrations of adrenaline, noradrenaline and dopamine were measured before and during chewing in two groups of betel quid and piper betel flower only, respectively.[24] Betel quid chewing caused a significant elevation in the concentrations of noradrenaline and adrenaline while piper betel flower chewing caused a moderate increase in noradrenaline without reaching statistical significance ($p = 0.06074$). It is generally believed that plasma noradrenaline concentration is an index of sympathetic nervous system activity, while adrenaline level is a response to sympathetic activation.[25] Therefore, the data suggest that betel quid chewing activates a sympathoadrenal response.

Comments and conclusions

Several claimed effects of betel quid chewing have been confirmed by objective psychophysiological or neurophysiological experiments. These effects include palpitation, sweating, a warm sensation of the body and face and heightened alertness. These studies demonstrated further that the effects of betel quid chewing was fast, with onset within 2 minutes after chewing, and reaching the maximal within 4–6 minutes, suggesting that active compounds released from betel quid chewing are absorbed mainly in the oral cavity, most probably through the mucous membrane, to account for the rapid onset.

It is interesting to note that the effects of betel quid chewing are habit-related and dose-dependent. The effects of betel quid chewing are stronger for fresh or occasional chewers than for habitual chewers, suggesting that tolerance or habituation also occurs in betel quid use. In RRIV study, consumption of one or two betel quids caused mainly a sympathetic activation while continued consumption of more than two betel quids showed a parasympathetic activation, thus indicating dose-related responses.

It was often difficult to be certain whether the sites of observed effects were peripheral or central. Although the cardio-acceleratory response may indicate peripheral sympathetic activation, it might be due to a central effect. Intravenous or subcutaneous administration of arecoline in human subjects, who were pretreated with a peripheral cholinergic blocker, caused a cardio-acceleratory response in all studies, and a pressor response in some.[7–10] These findings suggest that arecoline exerts a central cholinergic mechanism which then activates a descending sympathetic effect. In animal studies, arecoline has been shown to induce an arousal and EEG desynchronization, similar to the actions of ACh or by stimulation of the reticular activating system.[5,11]

On the other hand, arecoline and arecaidine from areca nut and several phenolic compounds from piper betle flower are found to be stimulators of catecholamine release from chromaffin cells *in vitro*.[14,15] Thus, the sympathetic effect of betel quid chewing may be due partly to the sympathetic actions of those alkaloids and phenolic compounds. Although betel quid chewing caused an elevation in the plasma concentrations of adrenaline and noradrenaline,[24] the sites of activation could not be decided.

As the plasma level of noradrenaline is believed to be an index of sympathetic nervous system activity while the adrenaline level is a response to sympathetic activation,[25] betel quid chewing may lead to a mobilized state similar to activation of the sympathoadrenal axis, which plays an important role in the adaptive preparation of the organism in emotional or stressful situations. This effect may partly explain the facts that betel quid chewing may reduce hunger and fatigue and increase the capacity for work.

Although arousal has been shown to be mediated by central cholinergic mechanisms, adrenergic drugs such as amphetamine are also capable of producing arousal.[26] The finding that the hyperthermic response from betel quid chewing was abolished by atropine and partly inhibited by propranolol suggests that there may be central and peripheral activations of sympathetic system.

In conclusion, the main effects of betel quid chewing appear to act upon the central and autonomic nervous systems although the sites and modes of these actions still remain poorly understood. These studies have confirmed some of the effects claimed by betel quid users, but further studies are required to determine more precisely the respective roles played by central and autonomic nervous systems and the individual pharmacological effects of the components of the betel quid mixture.

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