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Sex Specific Differences in GABA and Glutamate Levels in Response to Cigarette Smoke

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Abstract

Cigarette smoking act differently in men and women. Nicotine is the main psychoactive substance of tobacco and affects several neurological pathways through nicotinic acetylcholine receptors (nAChRs). Addiction to nicotine is developed by dopaminergic system with the involvement of GABAergic and glutamatergic systems. In the present study we have measured the circulating GABA and glutamate in smokers and non-smokers men and compared them with women. Our results showed that GABA levels are significantly less in men than women with greater difference among smokers. No difference was found in glutamate levels in men and women.

Keywords: Nicotine; Nicotinic acetylcholine receptors; Gamma-Amino Butyric Acid (GABA); Glutamate

Introduction

Men and women behave differently in response to cigarette smoke. Women are quicker to develop nicotine tolerance than men [1] and have higher rate of relapse [2,3]. Nicotine, a major substance of smoke binds to nicotinic acetylcholine receptors (nAChRs); ligand-gated cation channels [4] and modulates its activity. Nicotine also up-regulates nAChRs, which is more readily reflected in males than females [5].

Chronic smoking also alters circulating sex-hormones [6], which in turn mediates nAChRs activity. Progesterone has been shown to inhibit nAChRs activity [7] and estrogen but not testosterone can block antinociceptive effect of nicotine in female mice [8,9].

Although, dopaminergic system is involved in nicotine addiction, involvement of glutamatergic and GABAergic system is crucial for long term addiction [10]. GABA and glutamate are major inhibitory and excitatory neurotransmitters and are involved in many neurological pathways [11,12]. Nicotine modulates release of GABA and glutamate through nAChRs [13].

This study aims to measure gamma amino butyric acid (GABA) and glutamate in men and women chronic smokers of African American (AA) descent. GABA is known to control dopamine release through receptors present on dopamine releasing neurons while Glutamate, a neurotransmitter associated with memory in the brain, causes increase in alertness and pleasure through acetyl choline and dopamine, respectively [14].

Materials and Methods

Sample collection

Blood samples were collected in sterile condition from 58 African American men and women volunteers as per the institutional guidelines and grouped on the basis of smoking behaviour. Plasma were separated from these samples by centrifugation for 10 min and stored at -20°C in aliquots until further use. Enzyme Linked Immuno-Sorbant Assay (ELISA) kits were purchased from Alpco, Salem (NH).

Plasma concentrations of GABA and Glutamate

Plasma levels of GABA and Glutamate were measured by ELISA according to manufacturers' instructions. Plates were read in EPOCH Elisa reader from Biotek (Winooski, VT) following manufacturers' protocol and data were analyzed using GEN5 software.

Statistical analysis

All the results were compared using students' paired T-test. To determine whether significant difference in changes were present between groups, ANOVA was performed with a set to 0.05. All data are reported as mean ± SE.

Results

Plasma level of GABA is significantly decreased in male smokers (81.2 ± 2.4 ng/ml as against 122.2 ± 2.8 ng/ml) but not in female smokers (129.4 ± 4.0 ng/ml as against 136.5 ± 2.0 ng/ml), while Glutamate levels are decreased significantly in both males (10.5 ± 5.0 µg/ml as against 19.4 ± 2.9 µg/ml) and females (13.7 ± 3.3 µg/ml as against 19.3 ± 3.1 µg/ml) when compared to non-smoking volunteers of same sex (Figure 1).

When concentrations of thses neurotransmitters were compared between men and women, we found significantly lower levels of GABA in men than women. The difference is highly significant in smokers. No significant difference was found in the levels of glutamate between men and women.

Discussion

In the present study, we analyzed effect of gender and cigarette smoking on circulating GABA and glutamate in African-American smokers and non-smokers. Our results showed that GABA levels are significantly lower in men as compared to women irrespective of their smoking behavior. However, smoker men showed further decrease in GABA level but no significant changes were observed in smoker women when compared to non-smokers.

Our results correlated with the study by Esterlis et al. [15], who

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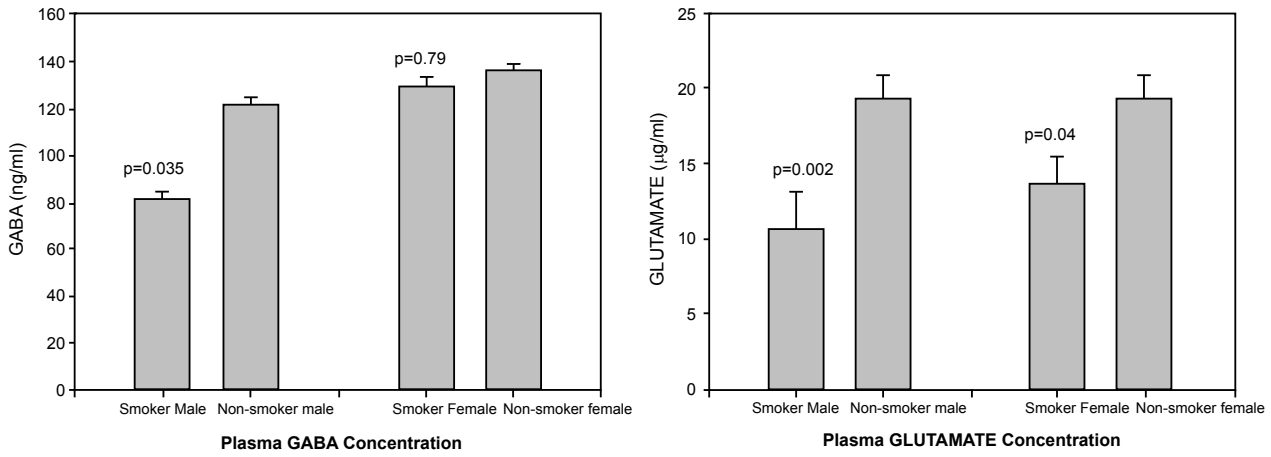

Figure 1: Plasma level of GABA and GLUTAMATE concentration between male/female smokers/non- smokers.

reported higher $GABA_A$-BZR availability in brain of women than men, regardless of smoking status but in complete contrast to study by Epperson et al. [16], where lower GABA levels are reported in female smokers but not in male smokers, when compared to corresponding non-smokers. This gender specific difference is more evident by the fact that during hippocampus development, switch from depolarizing to hyperpolarizing $GABA_A$ receptor mediated response occur earlier in females than males [17].

In addition to transient increase in GABAergic transmission, nicotine also enhances glutamatergic transmission through nAChRs [18], that desensitize them and ultimately effect on dopaminergic neurons. We didn't observe any sex-specific difference in glutamate levels. This may be a reason for lack of literature for gender specific studies on glutamatergic system. In an unrelated study Yararbas et al. [19] reported that nicotine induces conditioned place preference (CPP) through glutamate receptors in male rats but not in female rats.

For our study we collected samples randomly and didn't account for menstrual phase of women subjects. Thus, the effects of hormonal changes of women were not considered in this study. With these results we conclude that GABAergic system differs significantly between men and women but that difference is not evident for glutamatergic system.

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