Effect of nicotine on glutamatergic and GABAergic neurotransmission in developing brain

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Introduction
Nicotine facilitate release of neurotransmitters glutamate, GABA, dopamine, etc and thereby mediating the complex actions of nicotine addiction1. These neurotransmitters play major roles in glucose and energy metabolism, cortical excitability and cognitive function. Nicotine is rapidly absorbed into the blood stream, reaches the fetus at concentrations equal to or higher than those in the mother and activates nicotinic acetylcholine receptors in the peripheral and central nervous system2. Nicotine induces alterations in development of central neurotransmitter systems3. Maternal smoking during pregnancy is associated with a number of adverse behavioral and cognitive outcomes in the offspring. However, the underlying mechanism responsible for neurological changes associated with nicotine exposure during gestation and lactation is not properly understood. In this study we have investigated the effect of nicotine on cerebral metabolism during gestation and lactation period in mouse model.

Materials and Methods
All animal experiments were performed under approved protocols by the Institute Animal Ethics Committee. Female C57BL6 mice were treated with nicotine 0.5 mg/kg two times a day during gestation/lactation period. Control mice received normal saline for the same period. Metabolic measurements were carried out at postnatal day 25. Overnight fasted pups were anesthetized with urethane and infused with [U-13C6]glucose and [2-13C]acetate for 20 min4. At the end of the experiment, brain was frozen in situ in liquid N2. Metabolites were extracted from frozen tissues of different brain regions5. The 1H-(13C)-NMR and 13C-(1H)-NMR spectra of the tissue extracts were acquired at 600MHz (Bruker AVANCE) NMR spectrometer for the measurement of percent 13C labeling and isotopomer analysis, respectively. Contribution of [U-13C6]glucose and [2-13C]acetate for the total measured 13C labeling of amino acids were calculated by using isotopomers data.

Results and Discussions
Level of GABA and glutamine was decreased significantly (P<0.04) in cortex and subcortex in pups exposed with nicotine while glutamate, taurine and choline were increased significantly (P<0.05) in cerebellum.

The increase in GluC4 labeling from [U-13C6]glucose in cortex with nicotine suggests increased neurotransmission while an increase in labeling from [2-13C]acetate indicates an up-regulation of astroglial function in cortex and cerebellum. There was no significant change in flux through GABAergic pathways. These findings suggest that exposure with nicotine during gestation and lactation has profound effect on the development of glutamatergic neurons and astroglia in central nervous system.


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