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Tobacco smoking and nicotine modulate Nrf2-BDNF-Dopaminergic signaling in cerebral cortex and testis of adult rats during addiction and withdrawal**Nibedita Naha**

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Statement of the Problem: Tobacco smoking (nicotine) is associated with addiction behavior, drug-seeking and abuse. Several organ systems can also be affected by nicotine/smoking. However, the mechanisms that mediate this association especially, the role of brain-derived neurotrophic factor (BDNF), dopamine (DA) and nuclear factor erythroid-2 related factor-2 (Nrf2) signaling in the cerebral cortex as well as local neurochemical system in the testis, are not fully known.

Aim: The aim of the present study is to explore the toxic consequence of short- and long-term exposure and withdrawal in adult rodent models.

Methodology: We treated male Wistar rats with different doses of oral nicotine and passive smoking for 4-week (short-term) and 12-week (long-term) duration, where doses closely mimic the human smoking scenario. Also, in the precipitated withdrawal model, nicotine acetylcholine receptor blocker Mecamylamine, was given intraperitoneally after nicotine treatment followed by biochemical, immune-histological, molecular and statistical analyses.

Findings: The dose- and time-dependent anxiogenic and depressive behavior and cognitive interference are associated with neurodegeneration and DNA damage in the cerebral cortex from layer II onwards upon exposure to nicotine/smoking. Further, the dose- and time-dependent loss of developing spermatogonia and spermatocytes of the seminiferous tubules, disruption of basement membrane and DNA damage, results in low sperm count by smoking/nicotine treatment. Upregulation of pro-oxidants, i.e., reactive oxygen species and inducible nitric oxide synthase (iNOS), over-expression of BDNF, DA and DA marker, tyrosine hydroxylase are linked with concomitant downregulation of antioxidants i.e., ascorbate and Nrf2 in both the exposed cerebral cortex and testis. High serum cotinine of the exposure models of short and long durations are found to be reversed in the withdrawal model. Also, the reversible expressions of Nrf2, iNOS, DA and DA receptor along with tissue architecture are observed in the same area of the cerebral cortex and testis during Mecamylamine treatment, probably due to inhibition of nicotinic effects on both the tissues by releasing pituitary gonadotrophins. However, BDNF expression is not affected by Mecamylamine in the present study, as BDNF might follow differential response pattern upon nicotine withdrawal.

Conclusion & Significance: The intervention of BDNF-DAergic signaling and depletion of antioxidants are important factors in pathogenesis of the cerebral cortex and testis during nicotine/tobacco smoking, leading to neurobehavioral and reproductive impairments respectively, which are counteracted by Mecamylamine, resulting in reversal of nicotine-induced tissue lesion upon withdrawal through upregulation of Nrf2-ARE-mediated transcription mechanism. Thus, our results confirm the beneficial role of the receptor blocker in local BDNF-DAergic circuit of the testis and cerebral cortex that could underpin the novel therapeutic approaches targeting tobacco smoking/nicotine's neuropsychological disorders including drug addiction.

Biography

Nibedita Naha has her expertise in molecular approach of reproductive toxicology and neurotoxicology, cell signaling and RNA interference using animal models and human subjects with respect to occupational exposure. She has a passion in improving the health and wellbeing through her research findings in the respective fields since 2000. She is the recognized PhD Guide and Reviewer and Editorial Member of several international and national peer-reviewed journals. She is also the CPCSEA nominee for monitoring animal experiments in several research organizations and pharmaceutical companies in India, selected by MoEF, Government of India. She has authored 25 research articles. She has one international patent based on her Post-doctoral research. She is also the Life Member of several national and international scientific societies, Elected Member of PSI and Advisory Board Member of some national conferences.

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