

Maternal Normobaric Oxygen Partially Ameliorates Offspring Behavioral and Neuronal Dysfunction Following Lactational Cigarette Smoke Exposure

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Abstract

Maternal smoking and secondhand smoke exposure during lactation remain important public health concerns and are increasingly recognized as risk factors for adverse neurodevelopmental outcomes in offspring. However, the underlying neuronal mechanisms and effective intervention strategies remain incompletely understood. The present study investigated the effects of lactational cigarette smoke exposure (LCE) on offspring behavioral phenotypes and neuronal activation and evaluated the protective effects of normobaric oxygen (NBO) intervention. A mouse model of LCE was established using C57BL/6J dams exposed to cigarette smoke (10–15 mg/m³ total particulate matter, 3 cigarettes/day, 30 min/day) throughout the 3-week lactation period. A subset of smoke-exposed dams simultaneously received NBO treatment ($39 \pm 1\%$ O₂, approximately 100 kPa, 2 h/day). Offspring survival and body weight were monitored during development, while behavioral phenotypes were assessed during adolescence using the Open Field Test, Elevated Plus Maze, Tail Suspension Test, and Forced Swimming Test. Neuronal activation was evaluated in adulthood by c-Fos immunofluorescence and co-labeling analyses with NeuN, GAD67, and VGLUT2. Compared with control offspring, LCE offspring exhibited transient growth restriction during early postnatal development and developed hyperactivity-like and anxiety-like behavioral abnormalities during adolescence. NBO intervention significantly ameliorated these behavioral deficits. Immunofluorescence analyses revealed reduced c-Fos expression in multiple brain regions, particularly in the paraventricular nucleus of the hypothalamus (PVA) and basal ganglia (BG), indicating impaired neuronal activation. Further analyses demonstrated decreased c-Fos expression in NeuN-positive neurons. Moreover, LCE significantly reduced activation of GAD67-positive inhibitory neurons while increasing activation of VGLUT2-positive excitatory neurons, suggesting disruption of excitatory–inhibitory neuronal homeostasis. Notably, NBO treatment restored the activity of both inhibitory and excitatory neuronal populations toward control levels and partially normalized overall neuronal activation. These findings demonstrate that maternal cigarette smoke exposure during lactation induces persistent behavioral abnormalities and neuronal dysfunction in offspring through disruption of excitatory–inhibitory neuronal balance, whereas normobaric oxygen intervention partially restores neuronal homeostasis and ameliorates adverse behavioral outcomes, providing experimental evidence for a potential strategy to mitigate neurodevelopmental impairments associated with early-life tobacco smoke exposure.

Keywords

Lactational Cigarette Smoke Exposure, Normobaric Oxygen, Excitatory–Inhibitory Neuronal Homeostasis, Neurodevelopment, Behavioral Abnormalities