

## **Parental nicotine exposure elicits multigenerational nicotine preference and ADHD-like brain, behavioral, and epigenetic anomalies in adolescent mice**

Jordan M. Buck, Heidi C. O'Neill, and Jerry A. Stitzel

Parental nicotine (NIC) exposure (PNE) is associated with increased NIC use and neurodevelopmental disorders such as ADHD in adolescents. The present research addresses a void in the literature concerning the multigenerational effects of PNE on circadian and ultradian locomotor activity rhythms and anxiety-like/ risk-taking behaviors before, during, and after voluntary NIC consumption in the F1 (F1 NIC) and F2 (F2 NIC) generation adolescent offspring of mice exposed to NIC prior to and throughout breeding. The four-bottle choice test (FBCT) for NIC preference was conducted in an activity-monitoring home cage apparatus. FBCT results imply a predisposition to NIC consumption in F1 NIC and F2 NIC mice, coupled with NIC concentration-dependent generational differences in NIC preference. Home cage activity-monitoring data demonstrate ADHD-like anomalies in circadian and ultradian rhythmicity at baseline (BL) and during NIC consumption and withdrawal (WD) in F1 NIC and F2 NIC mice. ADHD-like home cage hyperactivity in F1 NIC and F2 NIC mice is attenuated by passive oral methylphenidate administration. Acute locomotor activity in a novel environment and anxiety-like/ risk-taking behaviors were assessed via the Open Field test (OFT) at BL and both prior to and following NIC WD. F2 NIC but not F1 NIC mice are hyperactive in the OFT and display an anxiolytic effect of voluntary NIC intake. Both F1 NIC and F2 NIC mice display increased risk-taking behaviors at BL, while F1 NIC mice alone exhibit an anxiogenic effect of NIC WD. Characterization of nicotinic acetylcholine receptors (nAChRs) in frontal cortex and striatum reveals down-regulation of nAChRs accompanied by dysfunctional nAChR-mediated dopamine release. Global DNA methylation analysis indicates methylome deficits in frontal cortex and striatum of F1 NIC and F2 NIC mice. Taken together, our data suggest that PNE enhances nicotine intake and precipitates multigenerational ADHD-like phenotypes that may be epigenetically mediated.

Research supported by National Institutes of Health (R21 DA040228; T32 DA017637)