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Underlying Mechanisms of the Effects of Nicotine in a Heritable Model of Drug Abuse Vulnerability in Psychosis

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Neonatal treatment to rats with quinpirole (NQ), a dopamine (DA) D2-like receptor agonist, significantly increases DAD2 sensitivity throughout the animal's lifetime, which is a hallmark of psychosis. Individuals with psychosis demonstrate a dramatic increase in cigarette smoking compared to the general population, resulting in deleterious health outcomes including a reduced life expectancy.: In recent work, we have reported an increased cortisol response in F1 generation offspring of NQ-treated rats via a bulk RNASeq analysis, suggesting that there is an increased sensitivity to stressful stimuli in this model. In addition, we have demonstrated enhanced nicotine conditioned place preference (CPP) in F1 generation animals. We hypothesized that F1 generation rats that are the offspring of NQ-treated founders will show: enhanced nicotine CPP reinstatement, an enhanced DA-ergic response to nicotine in neural circuitry which underlies drug reward; enhanced stress-induced nicotine CPP reinstatement; changes in DNA methylation patterns consistent with drug addiction. Experiment 1 revealed enhanced nicotine CPP reinstatement and an increased DA-ergic response in the NAcc shell of F1 generation rats given nicotine on CPP reinstatement. Interestingly, controls did not demonstrate nicotine CPP reinstatement, but also did not show increased DA activity in response to nicotine in the NAcc shell on CPP reinstatement. Experiment 2 revealed enhanced stress-induced nicotine CPP reinstatement in F1 generation animals compared to controls. Finally, MethylSeq analyses revealed a 22-fold enrichment in the nicotine addiction pathway in the IfL, and several consistencies with RNA Seq analyses. This study demonstrates vulnerability to nicotine addiction in a novel heritable model of psychosis.