Name: Russell W. Brown Email: brown1@etsu.edu

Analysis of the enhanced rewarding effects of nicotine and underlying neuroplasticity mechanisms in a heritable model of drug abuse vulnerability in psychosis

Russell W. Brown[1], Loren D. Peeters[1], Liza J. Wills[1], W. Drew Gill[1], Cynthia Vied[2], Justin T. Gass[1], Deirdre M. McCarthy[2], Pradeep G. Bhide[2]

[1]Department of Biomedical Sciences, James H. Quillen College of Medicine, East Tennessee State University, Johnson City TN 37614. [2]Department of Biomedical Sciences, Florida State University School of Medicine Tallahassee, FL 32306

Neonatal treatment to rats with quinpirole (NQ), a dopamine (DA) D_2-like receptor agonist, significantly increases DAD_2 sensitivity throughout the animal's lifetime. Increased DAD_2 sensitivity is a hallmark of psychosis. Individuals with psychosis demonstrate a dramatic increase in cigarette smoking compared to the general population. We bred NQ-treated rats to determine whether increases in DAD_2 sensitivity could be passed to the next generation (F1). In addition, we analyzed whether these animals would demonstrate enhanced conditioned place preference (CPP) to nicotine in adolescence and underlying mechanisms of this effect. We hypothesized that F1 generation offspring would demonstrate a genetic profile consistent with drug abuse vulnerability, enhanced nicotine CPP, deficits in sensorimotor gating as well as increased DAD_2 signaling and a sensitized response to brain-derived neurotrophic factor (BDNF) to nicotine in the nucleus accumbens (NAcc). RNASeq analyses revealed increased cortisol activity in F1 generation offspring of NQ-treated rats, consistent with drug abuse vulnerability. F1 generation offspring of at least one NQ-treated 'founder' demonstrated enhanced nicotine CPP, increased DAD_2 signaling and an enhanced BDNF response to nicotine in the NAcc, a brain region critical to drug reward. The DAD_2 receptor forms a heteromer with the metabotropic glutamate type 5 (mGlu5) receptor such that stimulation of the mGlu5 decreases DAD_2 signaling. Results revealed that a mGlu5 positive allosteric modulator alleviated nicotine CPP and sensorimotor gating deficits in F1 generation offspring of NQ-treated rats. This study establishes a novel model of drug abuse vulnerability consistent with psychosis and identifies a possible therapeutic target for treatment.