

Name: Britahny Baskin, Ph.D.

Email: b.baskin@northeastern.edu

Near-isogenic Spontaneously Hypertensive Rat Substrains Differ in Cocaine and Fentanyl Sensitivity and Self-Administration; Behavioral and QTL Analysis of Gene Expression (RNA, Protein) in an F2 Cross

Psychostimulant use disorders (PUDs) have resurged with increased use and overdose deaths, yet despite ~40-50% heritability, very few PUD-associated loci have been identified. Quantitative trait locus (QTL) mapping in F2 crosses between near-isogenic rodent substrains showing variation in addiction-relevant behavioral and molecular traits facilitates identification of causal genes. We previously found enhanced cocaine self-administration, impulsivity and compulsivity in SHR/NCrl vs. SHR/NHsd substrains purchased from their respective vendors (Charles River Laboratories, Harlan-Iotiv Laboratories). Here, we replicated and expanded on these observations using substrains bred in-house to exclude environmental explanations, characterize relevant ultrasonic vocalization signatures, and compare across drugs (cocaine vs. fentanyl) and sexes. Furthermore, we generated and tested a population comprising a reciprocal F2 reduced complexity cross to map QTLs underlying trait variation in novelty response and cocaine-induced locomotor sensitivity, RNA (eQTLs), and protein expression (pQTLs) from striatum and frontal cortex. For self-administration behaviors, adult rats from both substrains and F2 offspring were tested for acquisition of cocaine self-administration, motivation to acquire cocaine using FR1-FR5 schedules followed by a progressive ratio schedule with exponentially increasing required lever presses for each infusion. Different doses (1.0, 0.1, 0.03 and 0.01mg/kg) were then substituted to establish a dose-response curve and finally, rats completed extinction training and were assessed for cue-induced reinstatement. SHR/NCrl rats exhibited higher active lever responding than SHR/NHsd and consistently earned more infusions across different schedules of responding replicating the substrain's pro-addiction phenotype. Both groups extinguished responding to the same rate but SHR/NCrl rats reinstated lever pressing to a higher degree and emitted more ultrasonic vocalizations when exposed to drug-paired cues. In another cohort, we tested over 400 rats (SHR/NCrl, SHR/NHsd, and F2 offspring) through a two-week locomotor paradigm where they were exposed to saline injections followed by repeated cocaine or fentanyl injections. DNA was sequenced and analyzed with RNA and protein expression from striatum and frontal cortex of F2 rats. QTL analysis was performed in R/qtl and R/MatrixEQTL to triangulate on genetic loci and candidate genes underlying RNA, protein, and behavioral variation which identified a genome-wide significant QTL indicating a progressive increase in LOD score across repeated high-dose cocaine injections for cocaine-induced locomotion.

Authors:

Submitter: Britahny Baskin, Postdoctoral Research Associate, Northeastern University, Boston