Name: Sarah E. Swinford-Jackson
Email: sarah.jackson@rutgers.edu
PI Name: R. Christopher Pierce
PI email: chris.pierce@rutgers.edu

Epigenetic mechanisms underlying susceptibility to methamphetamine self-administration in methamphetamine-sired male rats

Sarah E. Swinford-Jackson[1], Azadeh Jadali[2], Mateo Sarmiento[3], Sharvari Mankame[1], Samantha J. Worobey[1], Kelvin Y. Kwan[2], Ronald P. Hart[2], and R. Christopher Pierce[1]

[1]Brain Health Institute and Department of Psychiatry, Robert Wood Johnson Medical School, Rutgers University; [2]Department of Cell Biology and Neuroscience, Rutgers University; [3]Center for Neurobiology and Behavior and Department of Psychiatry, Perelman School of Medicine, University of Pennsylvania

Preclinical evidence indicates parental exposure to drugs of abuse alters behavior and physiology of offspring. We previously demonstrated that when male rats self-administered cocaine, their male, but not female, progeny displayed reduced cocaine self-administration. Whether this drug resistance is similar in the offspring of sires who self-administer other psychostimulants, such as methamphetamine, has not yet been explored. Here, we tested the hypothesis that male, but not female, offspring of methamphetamine self-administering sires would self-administer less methamphetamine than saline-sired conspecifics. Sires self-administered methamphetamine and controls received yoked-saline delivery for 60 days and were mated with naïve females. Adult F1 offspring were allowed to lever press for intravenous methamphetamine (0.1 mg/kg/infusion) for 10 days on a fixed ratio 1 schedule. After two days on a fixed ratio 5 schedule, motivation for methamphetamine was assessed using a progressive ratio schedule over two days. Surprisingly, relative to saline-sired rats, male methamphetamine-sired offspring self-administered significantly more methamphetamine. Motivation for methamphetamine was also significantly higher in methamphetamine-sired vs. saline-sired male offspring. There was no difference in methamphetamine self-administration or motivation for methamphetamine in female offspring. The gene expression and open chromatin profiles of experimentally-naïve methamphetamine- and saline-sired male offspring were interrogated by single cell RNA-sequencing and ATAC-sequencing of the nucleus accumbens. These results suggest paternal methamphetamine use may confer increased drug taking in male offspring via epigenetic inheritance. Future experiments will interrogate the epigenetic profile in the sperm of methamphetamine sires for targets that may influence offspring gene expression.