Submitter name: Rebecca Prosser
Submitted email: rprosser@utk.edu

Paternal cocaine consumption in mice sex-specifically alters F1 offspring cocaine preference, circadian rhythm responses, and striatal gene expression.

Rebecca A. Prosser[1], Piet C. Jones[2,3], Daniel A. Jacobson[2,3], Alexandra M. Yaw[4] and J. David Glass[4]

[1]Dept. of Biochemistry & Cellular and Molecular Biology, and the NeuroNET Research Center, Univ. of Tennessee; [2]Biosciences Division, Oak Ridge National Laboratory; [3]Bredesen Center for Interdisciplinary Research, University of Tennessee; [4]School of Biomedical Sciences, Kent State Univ.

A growing body of research demonstrates that paternal cocaine leads to phenotypic alterations in offspring behavior and associated neural processing. We have investigated this utilizing a murine (C57BL/6J) oral cocaine model where sires consume cocaine for 40 days. We previously showed (Yaw et al., 2018) that this leads to sex-specific changes in circadian phase resetting in male and female (F1) offspring. Here we show that paternal cocaine intake decreases cocaine (but not ethanol or sucrose) preference in F1 male but not female mice bred from sires mated 24h after drug withdrawal/clearance, but not when sires are mated 4 months after drug withdrawal. RNAseq analyses from F1 nucleus accumbens tissue reveal significant increases and decreases in gene expression in male pups of cocaine-exposed sires, including many genes not previously identified in the context of addiction. Enrichment analyses highlight genes that can affect CNS development, synaptic signaling, extracellular matrix composition/function, and immune system function. Expression correlation analyses find that negative correlations far out-number positive correlations. They also identify one down-regulated gene, *Fam19a4*, with expression negatively correlated with many significantly up-regulated genes, as well as with many genes with expression not significantly altered by sire cocaine exposure. Collectively, these results reveal that paternal cocaine behavioral effects in F1 offspring may be due to epigenetic effects of the drug on the germline that are temporally limited to the period of sire cocaine exposure. The results also identify new cellular processes that may contribute to differential addiction propensity that we can investigate in future studies.