Submitter Name: Lisa Goldberg
Submitter email: lrg33@psu.edu
PI Name: Thomas Gould
PI email: tug70@psu.edu

IDENTIFICATION OF A LOCUS ON CHROMOSOME FOUR MEDIATING NICOTINE WITHDRAWAL DEFICITS IN HIPPOCAMPAL LEARNING

Lisa R. Goldberg[1], Munir G. Kutlu[1], Dana Zeid[1], Laurel R. Seemiller[1], Thomas J. Gould[1]

[1]Department of Biobehavioral Health, Penn State University

Cognitive deficits, such as disrupted learning, are a major symptom of nicotine withdrawal. These deficits are heritable, yet the genetic basis is unknown. Our lab has developed a mouse model of nicotine withdrawal deficits in learning, using chronic nicotine exposure via osmotic minipumps and fear conditioning. Previously, we identified differences between C57BL/6J and DBA2/J mice in cognitive deficits during nicotine withdrawal. Here, we aimed to utilize the BXD genetic reference panel to identify genetic variants underlying nicotine withdrawal deficits in learning. Male and female mice (n=6-11 per sex per strain, 31 strains) received either chronic saline or nicotine (6.3 mg/kg per day for 12 days), and then were tested for hippocampus-dependent learning deficits using contextual fear conditioning. Additionally, using GeneNetwork, we identified genetic correlations between nicotine withdrawal deficits in learning and locomotor stimulant response to phencyclidine (PCP) and cocaine, with strains that were less sensitive to stimulant withdrawal-induced cognitive deficits also being shown to be less sensitive to stimulant-induced increases in locomotor activity. Quantitative trait locus (QTL) mapping analyses using GeneNetwork (1000 permutations) identified a significant QTL on chromosome 4 (82.4 Mb, LRS =23.74, $p<0.05$). To prioritize candidate genes, we utilized publicly available hippocampal gene expression data from naive animals. We identified 4 positional candidates (*Ptprd*, *Tyrp1*, *2310067E19Rik*, *Nfib*) that overlapped with our behavioral QTL and correlated with our behavioral data. To expand upon these positional candidates and identify hippocampal transcriptome changes associated with nicotine withdrawal, we will soon complete mRNA-sequencing in the BXD lines exhibiting extreme phenotypic variation.