Name: Jacob Beierle (jbeierle@bu.edu)
PI Name: Camron Bryant (camron@bu.edu)
Presentation Preference: Oral

A BALB/c reduced complexity cross identifies Zhx2 as a candidate gene underlying oxymorphone brain concentration and state-dependent learning of oxycodone reward

Jacob A. Beierle[1,2,3], Emily J. Yao[1], Stan I. Goldstein[1], Julia L. Scotellaro[1], Katherine D. Sena[1], Olga Averin[4], David E. Moody[4],Christopher A. Reilly[4], Andrew Emili[5], Gary Peltz[6], Martin T. Ferris[7], Camron D. Bryant[1]

[1]Laboratory of Addiction Genetics, Department of Pharmacology and Experimental Therapeutics and Psychiatry, Boston University School of Medicine; [2]T32 Biomolecular Pharmacology Training Program, Boston University School of Medicine; [3]Transformative Training Program in Addiction Science, Boston University School of Medicine; [4]Department of Pharmacology and Toxicity, University of Utah, [5]Department of Biology and Biochemistry, Boston University School of Medicine; [6]Department of Anesthesiology, Perioperative, and Pain Medicine, Stanford University School of Medicine, [7]Department of Genetics, University of North Carolina

Understanding the pharmacokinetic profile opioid drugs is vital to therapeutic success, and mutations in human PK genes can drastically alter therapeutic efficacy of opioids. We observed that at 30 min post-oxycodone administration (1.25 mg/kg, i.p.), BALB/cJ mice showed higher whole brain concentration of oxycodone, and a female-specific increase in brain concentration of noroxycodone and oxymorphone compared to BALB/cByJ. This observation could explain an observed sex-specific increase in oxycodone state-dependent conditioned place preference in BALB/cJ females. To test for a link behavioral differences and PK differences, we conducted quantitative trait locus (QTL) mapping of whole brain oxycodone and metabolite concentrations in a reduced complexity cross (RCC) (N = 133 BALB/cJ x BALB/cByJ F2 mice). Because BALB/cJ and BALB/cByJ substrains differ by ~8,500 SNPs/indels, large genetic loci identified in an F2 cross are offset by a dramatic reduction in potentially causal variants. A single QTL for variation in brain oxymorphone was identified on chromosome 15 that explained 32% of the phenotypic variance in females. Oxymorphone is a full agonist at the mu opioid receptor more potent than oxycodone, and plausibly enhances oxycodone reward learning. Hippocampal and striatal cis-eQTL analysis revealed genetically regulated expression of *Zhx2*, a transcriptional repressor that harbors a private BALB/cJ retroviral insertion that dramatically reduces protein expression and leads to sex specific dysregulation of CYP450 genes within the liver. Whole brain mass spectroscopy proteomics in BALB/c substrains corroborated the Zhx2 eQTL. We hypothesize that decreased Zhx2 expression leads to increased CYP450 expression, increased brain oxymorphone, and increased oxycodone-induced behaviors.