Submitter Name: Jennifer Wolstenholme
Submitted email: jennifer.wolstenholme@vcuhealth.org

Adolescent binge ethanol slows oligodendrocyte maturation through regulation of histone methylation in the PFC

Emily Brocato[1], Ernesto Blay[1,2], Rachel Stevenson[1], Gabriel Elmisurati[1], A. Christian Pais[1,2], and Jennifer T. Wolstenholme[1,2]

[1]Department of Pharmacology & Toxicology; [2]Virginia Commonwealth University Alcohol Research Center, Virginia Commonwealth University

Binge drinking in adolescence is associated with reduced white matter and myelin in the frontal cortex. In mice, adolescent ethanol exposure decreased prefrontal cortex (PFC) myelin-related gene expression and genes that regulate the epigenetic mark, H3K9 tri-methylation (H3K9me3). H3K9me3 is a stable repressive mark primarily found in heterochromatin and is critical for the development of oligodendrocyte precursor cells into mature, myelin-forming oligodendrocytes. Given that binge ethanol decreased lysine demethyases specific for H3K9 methylation, this may be a mechanism through which ethanol decreases myelin expression in the frontal cortex. To uncover adaptive and maladaptive responses during the course of adolescent ethanol binges, we gavaged male and female DBA2/J mice with 4g/kg ethanol intermittently from PND 29-42 and collected frontal cortex 24 hours after 1, 4, or 8 ethanol binges. Oligodendrocytes were enriched from frontal cortex and compared to bulk PFC for expression of oligodendrocyte maturation markers and genes responsible for depositing or removing methyl groups from H3K9me3. In a separate cohort, we performed chromatin immunoprecipitation for H3K9me3 followed by PCR to determine H3K9me3 occupancy on genes known to be regulated during oligodendrocyte development. These data suggest sex differences during the course of ethanol exposure where males initially increase myelin gene expression while females decrease expression at the early exposures. By the end of the dosing paradigm, both sexes have decreased myelin expression. Additional ChIP findings are beginning to link these changes to an epigenetic mechanism for how ethanol disrupts oligodendrocyte maturation in the frontal cortex.