Adolescent binge ethanol alters oligodendrocyte maturation and regulation of histone methylation in the PFC

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Alcohol use in teens frequently begins at a young age, primarily occurs in binges, and is associated with cognitive impairments, reduced white matter content, and synaptic pruning in the frontal cortex. Ongoing brain development, particularly regarding frontal cortex myelination and synaptic connectivity, may make these adolescent drinkers particularly vulnerable to long-term consequences of binge ethanol. However, the molecular mechanisms underlying ethanol-induced myelin deficits in prefrontal cortex (PFC) development are not fully understood. We recently reported immediate and long-lasting transcript changes in the PFC following adolescent binge ethanol. Specifically, myelin-related genes and genes that regulate H3K9 methylation were decreased in the brains of adolescents after binge ethanol exposure. H3K9 methylation is a stable repressive mark primarily found in heterochromatin. H3K9me3 is also associated with the development of oligodendrocyte precursors into mature, myelin-forming oligodendrocytes. Given that binge ethanol decreased lysine demethyases specific for H3K9 methylation, this may be a potential mechanism through which ethanol decreases myelin expression in the frontal cortex. To uncover the immediate adaptive and maladaptive responses to adolescent ethanol, we dosed DBA2/J mice with binge-levels of ethanol (4g/kg, i.g.) intermittently from PND29-42. Tissue from the frontal cortex was collected at three time points during the course of binge ethanol administration: after 1 binge at PND 30, after 4 binges at PND 36, and after 8 binges at PND 43. Oligodendrocytes were enriched from frontal cortex and compared to bulk PFC for expression of oligodendrocyte maturation markers at each age by qPCR. We also tracked changes in genes responsible for depositing and removing methyl groups from H3K9me3 during the course of binge ethanol treatments. Together, these results will be the first to quantify changes in oligodendrocyte maturation during adolescent ethanol binges and link these changes to an epigenetic mechanism for how ethanol disrupts oligodendrocyte maturation in the frontal cortex.