

Adolescent binge ethanol alters histone methylation in the PFC leading to lasting memory deficits and increased ethanol sensitivity

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Alcohol use in teens primarily occurs in binges and is associated with cognitive impairments, reduced white matter content, and synaptic pruning in the frontal cortex. Binge drinking in adolescence increases rewarding aspects of ethanol while decreasing its aversive properties, enabling higher consumption and risk for alcohol use disorders. Ongoing brain development, particularly regarding frontal cortex myelination and synaptic connectivity, may make adolescent drinkers particularly vulnerable to long-term consequences of binge ethanol. However, the molecular mechanisms and genetic influences underlying ethanol-induced persistent changes in prefrontal cortex (PFC) development are not fully understood. To uncover these long-term adaptive and maladaptive responses to adolescent ethanol, we dosed DBA/2J and C57BL/6J mice with binge-levels of ethanol (4g/kg, i.g.) intermittently from PND29-42. Behavioral sensitivity to acute ethanol was assessed during adolescence and in adulthood to measure immediate and persistent effects of adolescent binge ethanol. As adults, mice were also tested for memory deficits. PFC mRNA expression was profiled in adolescents and adults to identify shared processes underlying the transition in the brain from adolescent binge ethanol to persistent behavioral changes in adulthood.

Inbred strains reacted similarly in ethanol-related behaviors. As adolescents, binge ethanol decreased ethanol sedative/hypnotic responses, but increased ethanol sensitivity in adults. Adolescent ethanol increased locomotor activity during anxiety tests without altering anxiety-like behavior. Cognitive deficits persisted in both strains when exposed to binge ethanol in a novel object test.

Genetic differences, however, were found in PFC transcriptional profiles. Binge ethanol decreased adolescent PFC myelin expression in DBA/2J, but not C57BL/6J mice. Genomic profiling of transcripts in DBA/2J PFC identified decreased expression of genes involved in histone demethylation at H3K9 and H3K36, epigenetic marks associated with active transcription and repression. H3K9me3 is also associated with the development of oligodendrocyte precursors into mature, myelin-forming oligodendrocytes. Given that binge ethanol decreased expression of genes involved in H3K9 methylation, this may be a potential mechanism through which ethanol decreases myelin in the frontal cortex and alters behavior in adulthood. These findings have important implications for addiction risk in humans and are beginning to identify underlying mechanisms and processes for how ethanol disrupts frontal cortex development.