Adolescent Binge Ethanol Induces Dysregulation of H3K36me3 at Dendritic Spine, Synaptic Assembly, and Memory-related Genes

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The prefrontal cortex (PFC) undergoes significant changes during adolescence, and alcohol exposure during this time is particularly damaging. Consuming alcohol, especially in binges, negatively impacts the adolescent brain, resulting in structural changes, decreased myelin, and lasting memory deficits. Gene expression changes in the PFC were measured by microarray to uncover the mechanisms in which ethanol induces these behavioral changes, and results showed that ethanol decreased the expression of chromatin remodeling genes responsible for the methylation of histone 3 lysine 36 (H3K36). H3K36me3 is present within the coding region of actively-transcribed genes, and safeguards against aberrant, cryptic transcription by RNA Polymerase II. These incorrect, cryptic transcripts disrupt normal levels of gene expression. Notably, H3K36me3 plays a critical role in memory consolidation and is increased in the PFC immediately after a Novel Object Recognition task (NOR). Conversely, decreases in H3K36me3 have been shown to cause deficits in NOR. We hypothesize that dysregulation of H3K36me3 could be responsible for the persistent memory deficits seen in adolescents exposed to binge ethanol. To investigate this, binge levels of ethanol (4g/kg) or water were administered to adolescent mice. Twenty-four hours after the last dose of ethanol, ChIP-sequencing for H3K36me3 was performed to determine the genes at which H3K36me3 occupancy was disrupted. Results showed that ethanol differentially impacted H3K36me3 binding to genes relating to memory, dendritic spine growth, and synapse assembly, providing preliminary evidence that dysregulation of this mark may underlie adolescent binge ethanol-associated memory deficits. Supported by NIAAA R01AA026347 to JTW and F31AA029259 to ERB.