

Adolescent Alcohol and Epigenetic Modifications: An Emerging vulnerability factor for Adult Psychopathology

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DNA methylation and histone acetylation/methylation are important epigenetic mechanisms that regulate gene expression. Epigenetic mechanisms have been implicated in neurodevelopmental disorders. Here, we examined the effects of adolescent alcohol exposure on brain epigenetic modifications and behavior phenotypes in adulthood.

Methods: Adolescent intermittent ethanol/n-saline (AIE/AIS) exposure in rats during post-natal days (PND) 28-41 with a 2-day on/off paradigm was performed as described earlier by us (Pandey et al., 2015). Various epigenetic targets and related mechanisms in the amygdala as well as anxiety-like and alcohol drinking behaviors in adulthood were measured.

Results: It was found that DNA methyltransferase (DNMT), histone deacetylase (HDAC) activity, HDAC2 and DNMT3b expression, and histone lysine demethylating enzyme LSD1 were altered in the amygdala of AIE rats during adolescence; some of these changes persisted into adulthood. Neuropeptide Y, brain derived neurotrophic factor (BDNF) and activity regulated cytoskeleton-associated (Arc) protein expression along with several other synaptic plasticity-associated gene expressions were decreased in amygdaloid structures of AIE adult rats as compared to AIS adult rats. Interestingly, chromatin was condensed at the NPY, Arc and BDNF exon IV gene promoters in the amygdala of AIE adult rats most likely due to an increase in DNMT and HDAC function, and a decrease in LSD1 and LSD1+8a expression. Treatment with DNMT or HDAC inhibitors attenuated AIE-induced anxiety-like and alcohol-drinking behaviors in adulthood, and also relaxed the chromatin of NPY, Arc and BDNF genes in the amygdala.

Discussion: These results suggest that AIE produces an enduring dysregulation in epigenetic processes in the amygdala, which may serve as a vulnerability factor for anxiety and alcoholism in adulthood.

References: Pandey SC, Sakharkar AJ, Tang L, Zhang, H. Potential role of adolescent alcohol exposure-induced amygdaloid histone modifications in anxiety and alcohol intake during adulthood. *Neurobiology Dis* 2015 March 24th (epub ahead of print)

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