Prenatal alcohol exposure in embryonic mice induces histone and cell death-related chromatin changes in a strain-dependent manner

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1. BACKGROUND

Prenatal alcohol exposure (PAE) is an adverse early life event contributing to biological embedding of poor adult health outcomes (e.g. autoimmune disease, chronic ear infection, dementia)

PAE has been shown to cause a significant amount of cell death in the developing brain as well as other brain alterations

Ethanol alters epigenetic profiles in the brain of alcohol-exposed mammals, which may be an early event in Fetal alcohol spectrum disorder (FASD) pathology

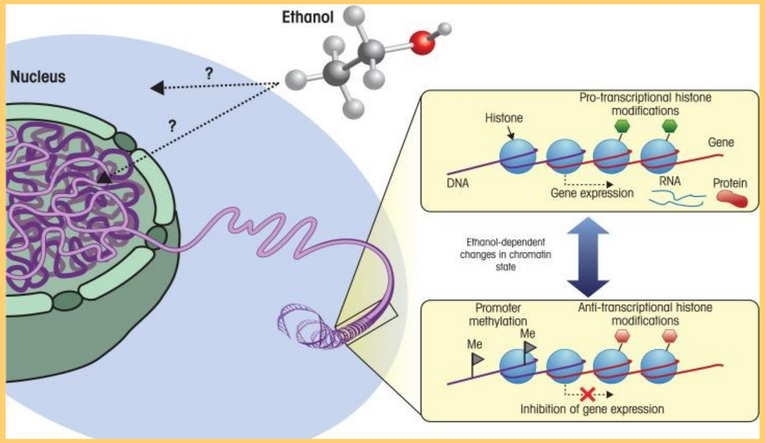


Figure 1. Environmental factors can cause changes in epigenetic landscape, which is characterized by DNA methylation, noncoding RNAs, RNA modifications as well as modification to the chromatin structure, such as histone posttranslational modifications (PTMs). Kobor and Weinberg, 2011

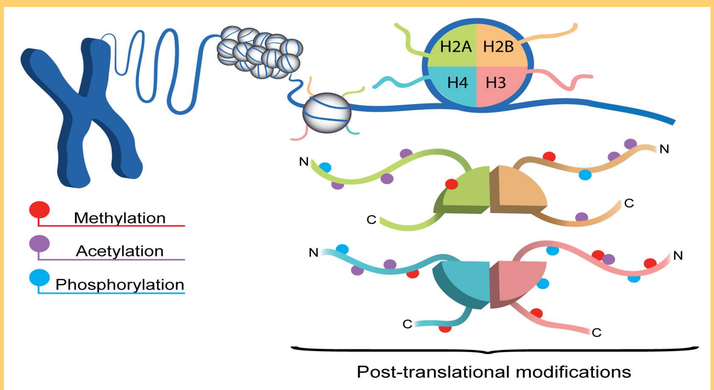


Figure 2. A histone modification is a covalent post-translational modification (PTM) to histone proteins which includes methylation, phosphorylation, acetylation, among others. The PTMs made to histones can impact gene expression by altering chromatin structure or recruiting histone modifiers. Histone modifications can act as mediators and signals for neural cell death following acute ethanol exposure.

PAE is known to alter histone modification in the brain at later developmental stages, but the early onset in the womb is still to be further elucidated.

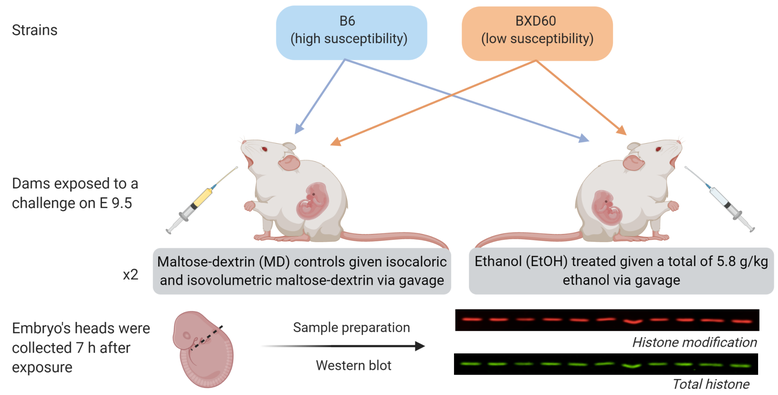
2. OBJECTIVES

1. Determine whether acute ethanol exposure alters histone PTMs and chromatin modification enzyme in the neural tube of embryonic mice.
2. Investigate the correlation between histone modification in the neural tube and strain susceptibility to ethanol exposure.

3. METHODS

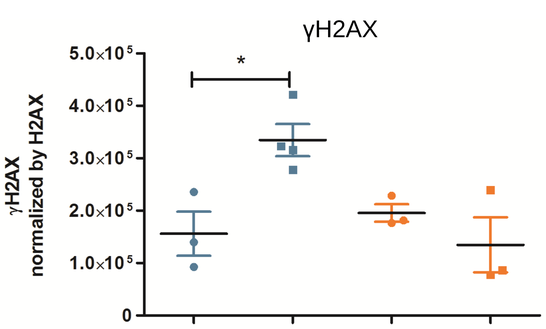
Here, we examined histone modifications, chromatin modifying and apoptotic events in relation to genetic background.

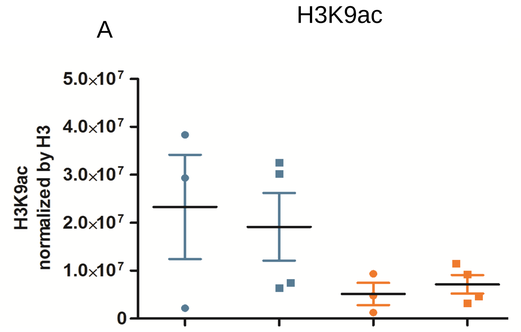
Mice were exposed to alcohol on prenatal day 9.5 (E9,5) – equivalent to 1st trimester.



4. RESULTS

Figure legends: ● MD control ■ EtOH B6 strain BXD60 strain





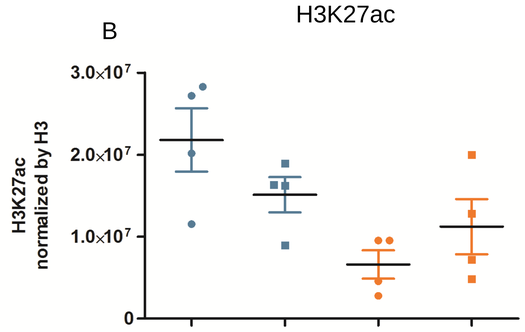
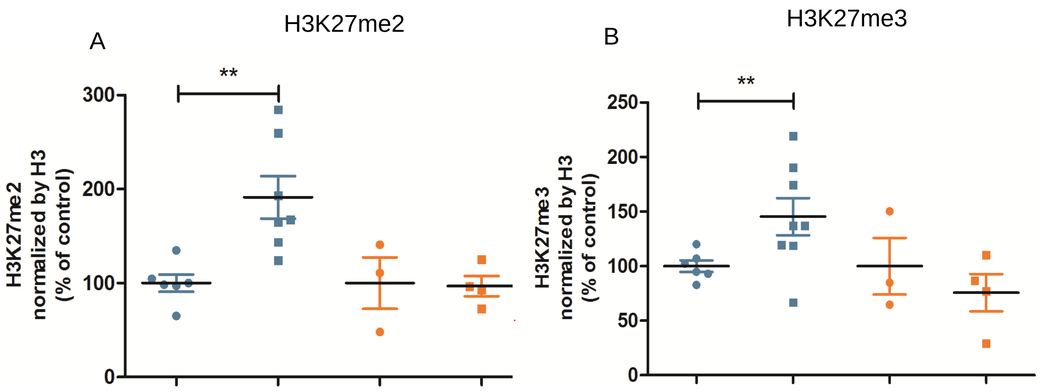


Figure 3. Strain-dependent response in histone mark related to cell death. H2AX contributes to nucleosome-formation, chromatin-remodeling and DNA repair, and is a mark for DNA double-strand breaks (DSB). Data are expressed as mean ± SEM for 4 biological replicates in each group. Different from control, *p < 0.05.

Figure 4. Strain-dependent outcome in histone acetylation. Neuronal tissue of Embryonic both mice strains exposed to ethanol showed no significant change to (A) H3K9ac and (B) H3K27ac in comparison to MD controls. Data are expressed as mean ± SEM for 4 biological replicates in each group.



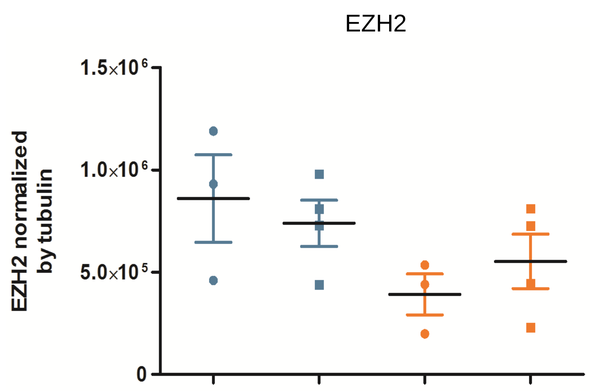


Figure 5. Strain-dependent outcome in histone methylation. Neuronal tissue of Embryonic B6 mice exposed to ethanol showed an increase in bulk levels of histone posttranslational marks often involved in the regulation of gene expression, such as (A) H3K27me2 and (B) H3K27me3 in comparison to MD controls. The BXD60 strain did not show any significant changes in the levels of the histone marks in the MD and EtOH groups. Data are expressed as mean ± SEM for 4 biological replicates in each group. Different from control, **p < 0.01.

Figure 6. Histone modification enzyme in the BXD embryonic mice exposed to acute ethanol. EZH2 participates in histone methylation and, ultimately, transcriptional repression.. Data are expressed as mean ± SEM for 4 biological replicates in each group. Different from control, *p < 0.05.

5. CONCLUSION

- Ethanol administration increased γH2AX in high susceptibility strain. This marker is widely distributed around double-strand breaks in the DNA and is a marker for apoptotic events.
- PAE induced histone PTMs changes, such as H3K27me2 and H3K27me3 and recapitulated effects seen by immunohistochemistry in mice brain regions.
- Further studies are necessary to understand the dynamics of histone modification enzymes in the embryonic mice exposed to acute ethanol.
- Together, these findings demonstrate that the levels of ethanol-induced effects on the expression of epigenetic marks occur in a strain-dependent manner and highlight the role of genetics in the epigenetic response to PAE.

6. ACKNOWLEDGMENTS

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