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Investigating Transcriptomic Responses to Ethanol Analgesia Over Time in C57BL/6J and DBA/2J Mouse Lines

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Purpose: Alcohol consumption produces analgesic effects, and people experiencing pain report drinking alcohol to alleviate discomfort. However, tolerance to analgesic properties of alcohol could drive escalating consumption. Understanding the genetic mechanisms of these processes could inform treatment options for people with AUD and pain conditions. This study characterizes the timecourse of genomic responses to ethanol analgesia.

Methods: B6 and D2 mice underwent basal hot plate or sham hot plate testing, followed by treatment with either ethanol (2g EtOH/kg) or saline via oral gavage. The hot plate assay was repeated 30 minutes post-gavage. Mice were sacrificed at 0.5hr, 4hr, or 24hr after the second hot plate test, and periaqueductal gray was harvested for RNAseq analysis. Differential gene expression (DEG) analysis and weighted gene co-expression network analysis (WGCNA) were performed with DESeq2 and WGCNA. Gene ontology (GO) analysis was conducted on DEGs and WGCNA modules.

Results: DESeq2 identified DEGs between ethanol treatment groups exposed to hot plate protocol. Clustering DEGs according to expression profiles produced gene clusters with similar regulation patterns. GO analysis of clusters upregulated in ethanol-receiving mice show enrichment for genes modulating GABA-gated chloride channel and GABA-A receptor activity. In D2 mice, ethanol-correlated WGCNA modules were enriched for genes regulating opioid receptor binding, neurotransmitter transport, and postsynaptic membrane. In B6 mice, aldehyde dehydrogenase activity-associated genes were enriched in a hot plate-correlated module.

Conclusions: An RNA-seq timecourse study of ethanol-induced analgesia using inbred mouse strains identified significant DEGs and gene modules correlated with ethanol analgesia phenotypes. *Supported by NIAAA R01AA027175, F31AA030918.*