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Mechanisms of Ethanol Anxiolysis: Role of Global Ninein Deletion on Ethanol and Anxiety-Like Behaviors

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Purpose: Anxiety disorders increase risk for Alcohol Use Disorder (AUD) and human subjects report that stress and anxiety increase ethanol consumption. The Miles laboratory previously identified Ninein (*Nin*) as a candidate gene underlying ethanol's acute anxiolytic-like properties in BXD recombinant inbred mice. Here we hypothesize that global *Nin* deletion will decrease basal anxiety, increase ethanol anxiolysis, and increase ethanol consumption.

Methods: *Nin* knockout mice were obtained from the International Mouse Phenotyping Consortium. Male and female mice wild-type (WT, $Nin^{+/+}$), heterozygous (HET, $Nin^{+/-}$), or homozygous (HOM, $Nin^{-/-}$) for *Nin* deletion were assessed for basal and acute abstinence anxiety-like behavior, acute ethanol anxiolysis, ethanol consumption, and ethanol sensitivity.

Results: There was no significant effect of sex or genotype on basal anxiety. Ethanol anxiolysis in the LDB showed a significant effect of genotype ($p = 0.014$) and treatment ($p = 0.002$) for percent time spent in the light (%TIL) and for percent distance traveled in the light (%DTL, genotype; $p = 0.043$, treatment; $p = 0.02$). 2BC-IEA studies showed no changes in ethanol intake (g/kg), but HOM animals exhibited a significant decrease in ethanol preference (%) compared to WT. During acute abstinence, only female HOM mice showed a significant reduction in %TIL ($p = 0.006$) compared to female WT mice.

Conclusion: These studies provide initial validation of Ninein as a gene modulating ethanol's anxiolytic properties and ethanol withdrawal-induced anxiety. Future experiments will investigate selective *Nin* deletion in central amygdala (CeA) on anxiety and ethanol-related behaviors.
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