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Effects of Chronic Alcohol Ingestion on Rat Lateral/Basolateral Amygdala Ligand-gated Chloride Channels

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Anxiety is a motivational component for many drugs of abuse, including ethanol. For example, acute ethanol reduces behavioral anxiety. This acute anxiolysis may be an underlying mechanism responsible for the co-morbidity¹ and familial segregation² of anxiety disorders and alcoholism. This anxiety-alcohol interaction is also represented during the withdrawal from chronic ethanol exposure that dramatically increases anxiety presumably due to adaptations in neurotransmitter systems governing this behavior. Indeed, increased anxiety is a common cause of relapse in abstinent alcoholics.³ Unfortunately, the neural basis for the relationship between ethanol-anxiety is not well understood. However, measures of heightened neuronal activity during ethanol withdrawal appear in the sensory, memory, and cognitive pathways regulating anxiety.⁴⁻⁶ To identify the cellular and molecular mechanisms regulating these relationships, we explored the functional adaptations to chronic ethanol ingestion using well-established liquid diet models^{7, 8} and whole cell patch clamp measures in acutely isolated lateral/basolateral amygdala neurons.

We have specifically examined GABA_A and strychnine-sensitive glycine receptors since manipulation of amygdala ligand-gated chloride channels can directly influence anxiety.⁹ GABA-mediated currents and current densities were significantly larger in neurons derived from animals that ingested chronic ethanol compared to cells from control liquid diet rats. Conversely, the magnitude of both glycine-mediated currents and glycine current densities did not vary significantly from control, suggesting that the chronic ethanol-induced alterations in lateral/basolateral amygdala ligand-gated chloride channels were specific for GABA_A receptors. Importantly, chronic ethanol exposure altered neither acute benzodiazepine efficacy nor acute ethanol sensitivity. During these studies, we noticed that the effects of acute ethanol on GABA_A responses from both control and chronic ethanol-exposed were modestly inhibitory. We explored the inhibitory actions of ethanol on lateral/basolateral amygdala GABA_A receptors by investigating the role of subunit composition in these acute effects. Specifically, we expressed GABA_A receptors composed of subunits that are highly expressed in the lateral/basolateral amygdala, namely $\alpha 1$, $\alpha 2$, $\beta 2$, and $\gamma 2S$.^{10, 11} Indeed, GABA currents mediated by $\alpha 2\beta 2\gamma 2S$ receptors were modestly inhibited by acute ethanol (100mM) while those containing the $\alpha 1\beta 2\gamma 2S$ subunits were modestly facilitated. These findings suggest that subunit composition may indeed influence the acute effects of ethanol on lateral/basolateral amygdala GABA_A receptors and ultimately determine their adaptive response to chronic ethanol exposure. Furthermore, the acute inhibition of amygdala GABA_A receptors by ethanol make it unlikely that direct action on this particular receptor system mediates the acute anxiolytic effects of ethanol. Conversely, the facilitation of GABA_A receptor function during chronic ethanol may be one mechanism by which ethanol maintains its anxiolytic potential during prolonged exposures.

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