Ethanol upregulates presynaptic Munc13-1 in hippocampus: A perspective in alcohol addiction

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Munc13-1 is a presynaptic protein which plays an essential role in glutamatergic synaptic vesicle priming. Our previous studies show that Munc13-1 binds to alcohol and modulates alcohol self-administration in *Drosophila*. However, it is not known whether alcohol has any direct effect on the Munc13-1 expression and glutamate release. Here, we examined the effects of ethanol on Munc13-1 expression in different model systems. First, we found that ethanol upregulated the expression of Munc13-1 in primary hippocampal neurons. We detected increased Munc13-1 expression together with unaltered vesicular glutamate transporter1 (VGLUT1), a marker of glutamatergic neurons, suggesting a possible role of Munc13-1 in maintaining glutamatergic synapses. Further, when we treated both wild type (WT) C57BL/6 and heterozygous Munc13-1 knockout (Munc13-$1^{+/-}$) mice with alcohol for 6 weeks (drinking in the dark paradigm, DID) we found that ethanol induced upregulation of Munc13-1 expression in VGLUT1 i.r. neurons in hippocampus of WT mice, whereas, expression of VGLUT1 remain unaltered. Furthermore, ethanol also compensated for the loss of Munc13-1 expression in Munc13-$1^{+/-}$ mice. Moreover, ethanol consumption interfered with the expression of glutamatergic NMDA and metabotropic receptors both at postsynaptic and presynaptic neurons. Taken together, we demonstrated ethanol-induced, upregulation of Munc13-1 and glutamate receptors in hippocampus possibly by interfering the glutamatergic neurotransmission. We conclude that Munc13-1 could be an important target in treating alcohol addiction. Supported by 1 R01 AA022414-01A1.