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CHRNA5 is Necessary for the Neuroadaptations Associated with Chronic Alcohol Exposure

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Polymorphisms in *CHRNA5*, the gene encoding the $\alpha 5$ subunit of neuronal nicotinic receptors (nAChRs), have been robustly associated with a number of smoking-related phenotypes. We recently showed that *Chrna5* deletion and the rs16969968 *CHRNA5* SNP modify the effects of chronic nicotine exposure and withdrawal on nAChR function in VTA dopamine (DA) neurons. We and others also showed that $\alpha 5$ -containing nAChRs influence alcohol reward and self-administration, and new evidence indicates that $\alpha 5$ -nAChRs are also implicated in the affective and physical signs of alcohol withdrawal. Furthermore, genetic variation in *CHRNA5* correlates with endophenotypes associated with alcohol use and abuse in humans.

Glutamate neurotransmission via the N-methyl-D-aspartate receptor (NMDAR) is central to the behavioral and neurophysiological effects of acute and chronic alcohol. Interested in examining the mechanistic role played by *CHRNA5* mutation in alcohol-related glutamatergic neuroadaptations, we treated WT and $\alpha 5$ mutant mice with 20% EtOH in the intermittent two bottle choice (I2BC) paradigm for 8 weeks. We found that chronic alcohol exposure reduces VTA NMDAR currents in DA neurons, an effect that persists during alcohol withdrawal. This reduction arises from synaptic incorporation of GluN3A-containing NMDA receptors (GluN3A-NMDARs). GluN3-NMDARs display decreased Ca^{2+} permeability and Mg^{2+} sensitivity, which are expected to alter the intrinsic excitability and plasticity of DA neurons. *Chrna5* mutation prevents these adaptations from taking place, suggesting a significant role of $\alpha 5$ -containing nAChRs in alcohol-related neuroplasticity. These results, together with our previous findings, have important implications for nicotine and alcohol co-abuse.