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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 α5 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 α5-containing nAChRs influence alcohol reward and self-administration, and new evidence indicates that α5-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 α5 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 Ca2+ permeability and Mg2+ 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 α5-containing nAChRs in alcohol-related neuroplasticity. These results, together with our previous findings, have important implications for nicotine and alcohol co-abuse.