Persistent Changes in the GluN2B-NMDA Receptor Proteome Following Chronic Adolescent Alcohol Exposure

T.A. Wills, M.L. Risher, K.M. Miller, H.S. Swartzwelder, D.G. Winder

Adolescent alcohol use is the strongest predictor for alcohol use disorders. In rodent models, adolescents have distinct responses to alcohol, some of which are known to persist into adulthood. In particular, adolescent intermittent alcohol exposure produces long lasting changes in hippocampal plasticity and dendritic morphology, as well as spatial memory impairment (Risher et al. 2015). One potential target for these effects is the alcohol sensitive GluN2B subunit of the NMDA receptor, which is known to be involved in synaptic plasticity and dendritic morphology. Additionally in humans there is an association between variants in the GluN2B gene, suicide attempts, and alcohol use during adolescence (Sokolowski et al. 2013). The current work set out to determine if there were persistent changes in the GluN2B-NMDA receptor proteome following adolescent alcohol exposure.

Methods: To do this, we employed a GluN2B-targeted proteomic strategy to identify signaling mechanisms altered by adolescent alcohol exposure that persist into adulthood. We collected adult hippocampal tissue (P70) from rats that were given either chronic intermittent adolescent alcohol exposure (2 weeks of intermittent, i.g. 5g/kg ethanol; P30-45) or control exposure (2 weeks of intermittent, i.g. saline; P30-45). This tissue was fractionated into synaptic and non-synaptic pools, IP'ed for GluN2B, and then underwent proteomic analysis.

Results: From these analyses we were able to identify a large number of proteins associated with the GluN2B proteome. Adolescent alcohol exposure produced a significant change in the GluN2B association with many proteins in both the synaptic and non-synaptic fractions. Some of these proteins include those involved in glutamate signaling, actin cytoskeleton signaling, and plasticity. Of particular interest, there was nearly double the amount of significant protein changes in the non-synaptic fraction as compared to the synaptic fraction.

Discussion: These data suggest that adolescent alcohol exposure may prime these signaling cascades to future alcohol exposures in adulthood.

References: Risher ML, Fleming RL, Risher WC, Miller KM, Klein RC, Wills T, Acheson SK, Moore SD, Wilson WA, Eroglu C, Swartzwelder HS (2015), Alcohol Clin Exp Res 39:989-997; Sokolowski M, Ben-Efraim YJ, Wasserman J, Wasserman D (2013), Molecular psychiatry 18:985-992.

Funding was provided NIH grants K99AA022651 for T.A. Wills, R01AA019455 for D.G. Winder, and U01AA019925 and VA Senior Research Career Scientist award for M.L. Risher, K.M. Miller, & H.S. Swartzwelder.