Persistent neuroimmune gene induction, Neurodegeneration and altered neurocircuitry following adolescent alcohol exposure.

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Adolescent alcohol abuse is common and causes life long changes in brain. Adolescent intermittent ethanol (AIE) exposure increases the expression of neuroimmune signaling molecules including high-mobility group box 1 (HMGB1), Toll-like receptor (TLR) 4, and proinflammatory cytokines. Adolescent alcohol-induced neuroimmune signaling is complicated by positive loops of multiple cytokine receptors and TLR signaling molecules that converge on nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB) and activator protein 1 that amplify and expand the expression of other neuroimmune genes. Ethanol increases brain neuroimmune gene expression through release of HMGB1 from neurons that activate TLR and other receptors leading to persistent long lasting increases in expression in adult brain. AIE leads to long lasting increases in adult neuroimmune gene expression as well as a loss of adult hippocampal neurogenesis and decreases in forebrain choline acetyltransferase (ChAT), the enzyme responsible for synthesizing acetylcholine. Studies of post-mortem human alcoholic brain find increased neuroimmune gene expression and decreased ChAT consistent with adolescent alcohol exposure contributing the alcoholic neuropathology. These changes in adult brain long after AIE exposure are associated with alterations in the adult brain responses to ethanol, e.g. decreased adult frontal cortical cFos and increased ventral striatal cFos ethanol responses. In addition, adults following AIE have reversal learning deficits consistent with prefrontal cortex dysfunction. Taken together, these findings suggest AIE causes persistent changes adult brain that could contribute to adult dysfunction and psychopathology. (Funded by the NADIA of NIAAA).