Title: Adolescent binge ethanol exposure produces protracted consequences on adult brain neuronal and innate immune ethanol sensitivity in male rats.

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Binge drinking (4-5+ drinks/2 hours) is prevalent in adolescents, and preclinical models of human binge drinking (adolescent intermittent ethanol; AIE) produce long-term consequences in the brain, despite abstinence. It is unclear how AIE affects the brain's response to ethanol later in adulthood. To address this, across peri-adolescence (postnatal days 25-54), male Wistar rats received a dose of EtOH (5 g/kg/day) or water (CON) on a 2-day-on/2-day-off schedule, followed by a multi-month period of abstinence. They underwent an EtOH challenge (EtOH 4.0 g/kg; water) in adulthood (PND 100-105), and were perfused 90 minutes later. Blood was collected for peripheral endocrine and immune markers (high mobility group box 1, HMGB1, and corticosterone, CORT). Brains were collected for immediate early gene expression (activity regulated cytoskeletal associated protein, Arc) and HMGB1. Results indicate that adult ethanol challenge decreased Arc+immunoreactivity (+IR) in the dentate and basolateral amygdala while increasing Arc+IR in the central amygdala of CON but not AIE rats. Similarly, adult ethanol challenge decreased HMGB1+IR in the dentate of CON but not AIE rats. HMGB1+IR increased in the basolateral but not central amygdala in AIE rats after adult ethanol challenge, suggesting brain regional specificity to innate immune and immediate early gene effects. Adult ethanol challenge increased plasma HMGB1 in control but not AIE-treated rats and CORT was increased follow acute ethanol regardless of AIE treatment. Findings suggest that AIE produces long-term consequences on brain and peripheral responsivity to ethanol, despite abstinence.