Differential effects of ethanol on cerebral cortical and hippocampal allopregnanolone levels in mice and rats

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Acute ethanol administration to rats stimulates the hypothalamic-pituitary-adrenal (HPA) axis and increases brain and plasma levels of the potent neurosteroid allopregnanolone. Increased allopregnanolone levels contribute to the anxiolytic, anticonvulsant, sedative and pro-aggressive actions of ethanol. It is not yet known if ethanol's effects on allopregnanolone levels generalize across species. Indeed, studies in mice have reported that ethanol does not always alter brain and plasma allopregnanolone levels We thus explored the effects of ethanol administration on brain levels of allopregnanolone and its precursor progesterone in C57BL/6J and DBA/2J mice, two inbred strains with different sensitivity to behavioral effects of alcohol.

Male C57BL/6J and DBA/2J mice were injected with ethanol (1, 2, 3 or 4 g/kg, i.p.) or saline and were sacrificed 1 hour later or 15, 30, 60 and 120 minutes later for the time course studies. Allopregnanolone, progesterone and corticosterone levels were measured by radioimmunoassay in cerebral cortex and hippocampus.

Acute ethanol administration did not alter cerebral cortical and hippocampal levels of allopregnanolone and progesterone in both C57BL/6J and DBA/2J mice at any of the doses examined. Cerebral cortical levels of allopregnanolone and progesterone were also not altered at any of the time points examined in either strain. In contrast, as expected, acute ethanol administration dose-dependently increased cerebral cortical levels of allopregnanolone and progesterone in male Sprague-Dawley rats. Acute ethanol administration dose-dependently increased corticosterone levels in the cerebral cortex and the hippocampus of both mouse strains. In C57BL/6J mice, corticosterone levels were increased by 319%, 352% and 448% in the cerebral cortex and by 284%, 218% and 368% in the hippocampus at the doses of 2, 3 and 4 g/kg, respectively, $p<0.001$. In DBA/2J mice, corticosterone levels were increased by 354%, 417%, 447% and 574% in the cerebral cortex and by 259%, 434%, 567% and 629% at the doses of 1, 2, 3 and 4 g/kg, respectively, $p<0.001$. The effect of ethanol on cerebral cortical corticosterone levels was also time-dependent: in C57BL/6J mice it was apparent at 15 min (+155%), reached a peak at 60 min (+306%) and remained elevated at 120 min (+217%) from ethanol administration ($p<0.001$); in DBA/2J mice it was apparent at 30 min (+546%), reached a peak at 60 min (+1002%) and remained elevated at 120 min (+822%) from ethanol administration ($p<0.001$). These results suggest that ethanol administration is activating the HPA axis, as expected, and that ethanol might directly impair brain neurosteroid synthesis. Moreover, to evaluate if the effect of ethanol on allopregnanolone levels was specific to ethanol or not, we tested whether administration of morphine, which also increases cerebral cortical levels of allopregnanolone in rats, alters allopregnanolone and progesterone levels in male C57BL/6J and DBA/2J mice. Morphine administration increased cerebral cortical allopregnanolone levels in C57BL/6J mice (+77%, +93% and +88%, at the doses of 5, 10 and 30 mg/kg, respectively, $p<0.01$) and DBA/2J mice (+81% at the dose of 5 mg/kg, $p<0.05$). Morphine administration also increased progesterone levels in both strains. These results suggest that the impairment in brain neurosteroidogenesis in C57BL/6J and DBA/2J mice appears to be specific to ethanol.

Overall, these results show important species differences in the effects of ethanol on brain neurosteroidogenesis. Given that ethanol does not alter cerebral cortical and hippocampal concentrations of allopregnanolone and progesterone in the two mouse strains examined, the differential sensitivity to some of the behavioral effects of ethanol cannot be directly correlated to hormonal changes in C57BL/6J and DBA/2J mice.