Adolescent social stress influences later ethanol and nicotine behaviors and microRNA expression

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**Background:** Epidemiological research has demonstrated an association between adolescent stress and increased alcohol and nicotine use, but the neurobiological mediators of this relationship are unknown.

**Rationale:** The goal of the current project was to develop an animal model to examine the effect of adolescent social stress on drug use and prefrontal cortex gene expression.

**Hypothesis:** We hypothesized that exposure to adolescent social stress would increase ethanol and nicotine consumption and that these effects might be mediated by changes in miRNA expression.

**Results.** Our results highlight gene by environment interactions. BALB/cJ mice exposed to adolescent stress were more sensitive to acute nicotine in late adolescence but consumed less nicotine in adulthood. In contrast, C57BL/6J mice had no long-lasting changes in these nicotine behaviors following adolescent social stress. Strain differences were also observed for binge-like ethanol consumption. BALB/cJ mice exposed to social stress during adolescence had decreased ethanol consumption in adulthood similar to the finding with nicotine consumption. In contrast, C57BL/6J mice exposed to social stress displayed increased ethanol consumption. Small RNA sequencing uncovered differentially regulated miRNA in the prefrontal cortex depending on stress condition which may provide a mechanism through which adolescent stress alters later drug behaviors.

**Conclusion:** These results suggest that adolescent social stress has long-term consequences on both ethanol and nicotine behaviors, but genetic background is critical. Further, stress-related changes in miRNA gene expression provide a mechanism underlying altered drug behaviors.