Adolescent Social Isolation Increases Alcohol Drinking and Anxiety-Like Behavior: Role for Disrupted Endocannabinoid Signaling in the Central Amygdala.

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Reduced social interaction during adolescence increases susceptibility to neuropsychiatric disorders in adulthood, including anxiety and alcohol use disorders (AUD), with adolescent females responding differently compared to males. Social isolation is a stressor with high human relevance, especially during the COVID-19 pandemic, when millions of adolescents faced prolonged periods of isolation. Both stress and cognitive neural systems undergo major developmental changes during adolescence, a critical period for maturation of the central nucleus of the amygdala (CeA). Dysfunction of GABAergic networks within the CeA during development increases vulnerability to affective disorders in adulthood. In this study, we investigated the impact of social isolation during adolescence on alcohol drinking and adult susceptibility to anxiety in both sexes, and the associated GABAergic synaptic changes in the CeA.

Methods: First, we assessed the impact of social isolation on voluntary alcohol drinking. Male and female rats were intermittently socially isolated for 24h prior to 2-bottle choice (2BC) access to alcohol (20% v/v, 2h/session) vs. water from PND28. After each drinking session, isolated rats were re-grouped until the next day, when they were isolated again. This protocol was repeated 3 times/week across 4 weeks. Grouped-control rats were housed 3-4/cage and exposed individually to 2BC 3 times/week. Second, we tested all rats for irritability-like symptoms by assessing aggressive- and defensive-like behaviors, after two weeks of abstinence from alcohol (PND70±2). Third, we used liquid chromatography-mass spectrometry to measure CeA endocannabinoid levels in abstinent rats (PND75±2). Lastly, we used ex vivo slice electrophysiology to characterize the GABAergic synaptic activity of CeA in abstinent rats (PND75±2).

Results: We found that social isolation during adolescence increases alcohol intake and preference. Males also show higher irritability-like behavior than females during post-adolescence abstinence from alcohol and social isolation significantly increases the number of aggressive signs, i.e., biting, selectively in males. We then used a lipidomic approach to quantify CeA tissue levels of endocannabinoids, anandamide (AEA) and 2-arachidonoylglycerol (2-AG). We found i) significantly reduced 2-AG levels in socially isolated rats; ii) lower levels of 2-AG in females compared to males; and iii) no sex- or isolation-dependent effects on CeA AEA levels. Lastly, we found that social isolation reduced spontaneous inhibitory postsynaptic currents (sIPSCs) frequency in males but increased sIPSCs frequency in female rats.

Discussion: Social isolation during adolescence (PND28-PND56) increases alcohol intake and preference in both males and females and aggressive-like behavior selectively in adult males. These behavioral changes are accompanied by dysregulation of GABAergic transmission in the CeA, possibly through 2-AG mediated mechanisms. A sex-dependent response to social isolation that alters inhibitory CeA synaptic activity during development may enhance susceptibility to emotional disturbance and AUD in adulthood and disrupted CeA 2-AG signaling might drive the lasting effects of adolescent isolation and alcohol use. My goal is to elucidate the specific underlying mechanisms and test components of the endocannabinoid system as a therapeutic target.

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