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P665. Altered δ Opioid Receptor Expression and Function Mediate Opioid Addiction Vulnerability After Early-Life Adversity

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Background: Early life adversity (ELA) is associated with vulnerabilities to reward-related problems, such as addiction to pro-hedonic opioid drugs. Women may be particularly vulnerable, suggesting a sex-specific derangement of reward circuit maturation by ELA. However, the mechanisms by which this occurs are poorly understood. To test the hypothesis that ELA perturbs the normal maturation and function of endogenous opioid systems, we employed a naturalistic model of ELA, in which bedding and nesting materials are limited during the first week of life, and examined the impacts of ELA on expression and function of opioid ligands and receptors and on opioid drug seeking behaviors in female rats.

Methods: Adult female ELA-experienced rats were tested for aspects of opioid addiction-like behaviors including free consumption and economic demand elasticity to measure motivation for opioid drugs ($n = 12$/group). To gain insight into ELA-induced molecular changes in reward-related regions, we employed RT-qPCR for a suite of molecular candidates ($n = 8$-9/group). Following on our intriguing molecular findings, we pharmacologically manipulated endogenous opioid signaling during opioid self-administration to test the mechanisms of ELA-enhanced opioid seeking ($n = 12$/group).

Results: ELA led to enhanced motivation for opioid drugs in female rats, in accord with our prior findings ($t(22) = 3.620$, $P = 0.0015$). RT-qPCR revealed a selective reduction in delta opioid receptor expression following ELA in basolateral amygdala ($t(17) = 3.197$, $P = 0.0053$), and no change in μ or κ receptor, nor in the endogenous ligands. Preliminary results from pharmacological manipulation of δ opioid receptors in BLA during opioid self-administration suggest a possible mechanism by which ELA may cause vulnerability to addiction.

Conclusions: ELA causes enduring changes in δ opioid receptor expression in amygdala, which may underlie the sex-specific pro-addiction phenotype in female rats. Unlike μ and κ, which are expressed at adult levels in neonatal rats, δ expression matures later, potentially rendering the receptor vulnerable to adverse early-life experiences. Understanding the mechanisms by which ELA promotes vulnerability to opioid use disorder is critical for identifying those at high risk for addiction and developing effective interventions for preventing opioid-related morbidity and mortality.

Keywords: Early-Life Adversity, Opioid Addiction, Delta Opioid Receptor, Basolateral Amygdala, Nucleus Accumbens

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