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Background: The epidemic of opioid use, addiction, and overdose is an ongoing public health problem in the U.S. Whereas opioid over-prescription and genetic predispositions play a in this epidemic, these factors alone cannot explain the exponential rise in opioid abuse. Individuals who have experienced early life adversity (ELA) such as poverty or abuse are overrepresented among opioid abusers, and addicted women report experiencing such adversity at a disproportionate rate, suggesting that they may be uniquely vulnerable to this risk factor. The mechanisms by which ELA confers increased vulnerability to opioid addiction are still poorly understood, and in humans, it is impossible to dissociate ELA from other co-existing vulnerabilities. Therefore, we employ a naturalistic ELA model in rats to examine the sex-specific impacts of ELA on reward and stress circuit development, and concomitant opioid drug seeking behaviors.

Methods: ELA was modeled in male and female Sprague Dawley rats by limiting bedding and nesting from postnatal day 2-9, whereas controls were housed in standard cages. As adults, rats were tested on intravenous heroin self-administration, extinction, and reinstatement, as well as in a measure of microeconomic demand elasticity for opioids. We assessed ELA-induced changes in reward- and stress-circuit nodes which might convey susceptibility to the addictive effects of opioids using two approaches(a) the activation of brain regions (nodes) of the circuit by heroin in naïve and in opioid-experienced animals. (b) gene expression changes in the same nodes/regions for a panel of reward- and stress-related molecules All experiments included 7+ rats per sex and rearing condition, and data were analyzed using t-test or ANOVA with Bonferroni post-hocs.

Results: ELA robustly increases opioid addiction-like behavior in female, but not male rats. Compared to controls, ELA females persisted in seeking heroin longer during extinction (e.g., number of days until extinction criterion $t12=2.509$; $P=0.0274$; $n = 7$/group), showed greater cue-induced (ELA vs. CTL active lever presses: $t24 = 4.676$; $P=0.0002$; $n = 7$/group) and heroin-primed reinstatement (ELA vs. CTL active lever presses: $t24 = 4.676$; $P=0.0002$; $n = 7$/group), and showed less elastic opioid demand, similar to a phenotype seen in humans addicted to opioids ($t28=2.630$; $P=0.0137$; $n = 15$/group). In contrast, ELA males did not exhibit opioid addiction-like behaviors. Preliminary findings suggest that ELA-induced opioid vulnerability in females may involve altered heroin-induced activity in nucleus accumbens, especially in a dorsomedial accumbens shell opioid "hedonic hotspot." Initial results also suggest sex-dependent changes in pleasure- and stress- related molecule expression in several of the nodes of the reward and stress circuits.

Conclusions: ELA produces a sex-specific pro-opioid addiction phenotype in female rats, which may be caused by disrupted neurodevelopment of reward and stress circuits, leading to aberrant neural responses to opioid drugs.

Keywords: Opioid Addiction, Early life Adversity, Reward Circuitry, Nucleus Accumbens, CRH

Disclosure: Nothing to disclose.