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Sex- and Region-Specific Impacts of Early-Life Adversity and Self-Administered Heroin on Transcriptomics and Addiction Vulnerability

Opioid use disorder (OUD) is a major public health crisis, and addressing it requires a deeper understanding of addiction's molecular mechanisms. We used a well-established model of early-life adversity (ELA) in outbred Sprague-Dawley rats to study developmental influences on heroin addiction vulnerability, and previously we discovered sex-dependent, addiction-relevant behavioral phenotypes, and alterations in protein expression in nucleus accumbens (NAc), amygdala (AMY), and prefrontal cortex (PFC).

Male and female rats were reared during a critical period for affective brain circuit development (postnatal days 2-9) in cages with limited bedding and nesting material, our established ELA paradigm, or in standard cages. In adulthood, rats were allowed to self-administer heroin for three days, then we conducted bulk RNA sequencing of PFC, NAc, and AMY. We also conducted preliminary single-nucleus RNA- and ATAC-sequencing analyses in NAc and AMY to probe cell-specific changes in transcription and chromatin accessibility that could underlie ELA-induced vulnerability to the addictive effects of opioid drugs.

Analyses identified gene- and gene network-level changes induced by ELA, heroin, or the combination, shedding light on biologically relevant pathways. Of particular note were signs of sex- and region-specific metabolic stress, as well as potential mitochondrial function changes elicited by ELA in females, and augmented inhibition in males. Initial heroin self-administration also induced profound changes in gene networks, as determined by weighted gene co-expression network analysis. These partially overlapped those seen in human OUD datasets, suggesting conserved molecular pathways. We also report initial validation of some of the most promising findings using protein- and mitochondrial function assays. Finally, we make available a list of biological samples available for distribution in collaboration, and links to tools that allow collaborators to explore these rich datasets.

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