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Differential gene expression and epigenetic regulation in the medial prefrontal cortex of rats showing vulnerability to opioid addiction

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Characterizing molecular mechanisms underlying individual differences in opioid addiction could inform more effective prevention and treatment strategies. We have found that the magnitude of Withdrawal-Induced Anhedonia (WIA) after acute morphine administration is negatively correlated with various measures of subsequent morphine self-administration (MSA). We are currently assessing how gene expression and chromatin accessibility in the medial prefrontal cortex (mPFC) vary in rats assigned to "High WIA" (i.e., low addiction vulnerability) or "Low WIA" (i.e., high addiction vulnerability) based on a median split of WIA magnitude. RNA-seq revealed greater changes in gene expression in High WIA rats (vs. Saline) in comparison to Low WIA rats (vs. Saline), which was also reflected by greater alternations in canonical pathways in High WIA rats. These changes were involved in gene networks associated with neural signaling, neural development/protection, neuroinflammation, and metabolism. In addition, two upstream regulators, TCF7L2 and SOX2, were identified in High WIA rats, suggesting an involvement of cholinergic gene regulation, insulin signaling and appetite. Since all WIA animals received identical opioid treatment, these changes reflect mechanisms underlying WIA itself rather than mere opioid exposure. HOMER motif analysis of ATAC-seq data revealed changes in accessibility after WIA of AP-1 family members including FOS, as well as EGR1 and MEF2D, which regulate AP-1 family genes. We are currently exploring other epigenetic marks (e.g., DNA methylation, histone modifications) using technologies, such as Third-generation Sequencing and CUT&TAG, to provide a more comprehensive understanding of mechanisms underlying opioid addiction vulnerability.