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Transcriptional Impact of Chronic Fentanyl Self-Administration on Habenula Circuits

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The habenula (Hb) modulates reward processing and pain/aversive states through its connectivity with midbrain structures, notably the dopaminergic ventral tegmental area (VTA). Hb dysfunction has been implicated in a variety of neuropsychiatric disorders, including substance use disorders. Hb expresses high levels of μ-opioid receptors, which mediate the analgesic effects of opioids. However, it is unknown how Hb cell types are transcriptionally impacted in opioid use disorder (OUD). To identify genes regulated by chronic opioid intake, we performed bulk RNA-sequencing (RNA-seq) on Hb tissue from rats exposed to an extended access fentanyl self-administration (SA) paradigm. Differential gene expression analysis identified 453 differentially expressed genes (DEGs, FDR < 0.05) associated with chronic fentanyl SA compared to saline controls. Gene ontology analyses implicated synaptic plasticity, glutamatergic, neuromodulatory, and neuropeptide signaling, and mitochondrial dysfunction. Cell type enrichment analyses using mouse and human single nucleus (sn) RNA-seq data revealed that upregulated DEGs were enriched in a unique lateral Hb neuronal subpopulation. This subpopulation, which was defined by expression of Kcnmb4, and also enriched for Oprm1, may represent a cell type that is particularly vulnerable to chronic opioid SA. We are now performing cell type- and circuit-specific molecular profiling follow up studies. Molecular genetic labeling of VTA-projecting Hb neurons revealed that a subset expresses Oprm1. By combining these circuit labeling techniques with snRNA-seq, we obtained transcriptomic signatures for VTA-projecting Hb neurons and evaluated their enrichment in fentanyl-responsive genes. These studies are expected to provide new molecular insights into the contribution of Hb dysregulation to OUD.