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Characterization of opioid-induced gene expression in discrete habenula cell types and projection neurons

The opioid epidemic is a significant public health crisis requiring accelerated efforts to translate mechanistic studies into therapeutic developments. Substance use disorders feature dysregulation of brain reward circuits, especially dopaminergic systems governing motivated behavior. The habenula (Hb) is an “anti-reward” center that sends projections to the ventral tegmental area (VTA) and other aminergic centers to modulate reward seeking. Hb circuit dysfunction is associated with addiction, but the underlying molecular mechanisms, especially in the context of opioid use disorder (OUD), are unknown. Here we generated single nucleus RNA-sequencing (snRNAseq) data from the rat Hb following chronic long access fentanyl self-administration. In parallel, we profiled Hb neurons projecting to the VTA to define their unique molecular profiles. We integrated these datasets to understand how Hb populations, particularly Hb-VTA projection neurons, are impacted by fentanyl at the molecular level and how this relates to behavioral measures. We identified candidate transcriptomic signatures and gene regulatory mechanisms that mediate cell type-specific responses to fentanyl within the medial and lateral habenula. We further integrated these findings with genome wide association studies of OUD as well as human single cell and spatial transcriptomics Hb datasets to map how populations associated with OUD risk and opioid response are topographically organized in the Hb. Together, these findings reveal transcriptomic signatures associated with opioid intake and risk for OUD in spatially discrete Hb cell types and circuits, which can inform future functional studies and help translate insights from rodent models into cell type- and circuit-based therapeutic strategies for OUD.

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