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Connectome- and Transcriptome-based Approaches to Decode Circuit-Specific Mechanisms of Addiction

Background: The interpeduncular nucleus (IPN) is an understudied midbrain region relaying information between the limbic forebrain and brainstem. IPN neurons are highly heterogeneous and can be subdivided into functionally distinct populations based on transcriptomic and signaling profiles. These neurons utilize a diverse set of signaling factors. The IPN is densely vascularized, with neurons often clustering around blood vessels and forming foot-like expansions. This specialized morphology suggests these neurons may detect circulating hormonal signals and perform neurosecretory functions. Emerging evidence suggests the IPN plays an important yet not fully understood role in maladaptive behaviors related to substance use disorder (SUD). These findings emphasize the need for transcriptomic, connectomic, and functional characterization of the IPN to define how specific neuronal subsets drive SUD-related behaviors.

Method: We used adult C57BL/6J, Four Core Genotype, and gonadectomized mice, both males and females. Analyses included 10x Genomics scRNA-seq for transcriptomics, MAPseq for single-cell connectomics, and whole-cell patch-clamp for synaptic activity. Additionally, in vivo photometry quantified glutamate and acetylcholine release simultaneously in freely behaving mice.

Results: Using Visium, we identified the IPN as the midbrain region with the highest density of sex-dependent differentially expressed genes (DEGs). scRNA-seq further revealed that chronic opioid exposure induces sex-specific transcriptomic plasticity in the IPN. Through MAP-seq and pathway-specific recordings, we identified sex differences in the IPN-to-medial raphe (MR) circuit's connectivity and synaptic strength. Finally, we determined that these circuit differences are driven by gonadal hormones rather than sex chromosomes. Dual-sensor in vivo photometry revealed that glutamate and acetylcholine exhibit distinct signaling patterns in response to substances of abuse.

Conclusion: Single-cell and connectomic profiling identify the IPN as a key site of sex-dependent opioid adaptation. These results define a novel non-mesolimbic framework for understanding sex differences in SUD.

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