

A novel cellular and circuit target for opioids

Opioids actions at mu opioid receptors (μ ORs) in the nucleus accumbens (NAc) are critical for opioid reward and reinforcement. Although recent transcriptomic studies reveal that μ OR (Oprm1) expression is unevenly distributed among subpopulations of medium spiny neurons (MSNs) in the NAc, the identity and contributions of distinct Oprm1-expressing neurons to opioid-related behaviors remains poorly defined. Recently, we leveraged available transcriptomic datasets to identify a transcriptionally distinct Oprm1-expressing MSN population, marked by mRNA for the carbohydrate sulfotransferase Chst9. Here, we extend these observations with additional single nucleus RNA-seq and Xenium spatial transcriptomics profiling to further define gene expression patterns and anatomical localization of this unique population. Notably, while comprising ~7% of NAc cells, Chst9-MSNs express over 35% of Oprm1 transcripts within the NAc. Further, this neuronal population is conserved in the NAc of mice, rats, non-human primates, and humans, and expresses other genes previously linked to reward and aversion. Xenium analysis of mouse NAc revealed that Chst9-MSNs are concentrated in discrete islands in the medial and ventral regions of the NAc shell. Using a custom Chst9-Cre-tdTomato transgenic rat, we performed the first identified electrophysiological recordings from Chst9-MSNs, demonstrating robust silencing of this cell population by the μ OR agonist DAMGO. In order to examine a potential role for this cell type in opioid reward and reinforcement, ongoing experiments are using a CRISPR-based strategy for conditional Oprm1 deletion in Chst9-MSNs. Together, these findings identify a transcriptionally and spatially defined subpopulation of Oprm1-enriched MSNs, and provide new insights into the cell-type-specific action of opioids.

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