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Dissecting the functional roles of GABAergic vs. glutamatergic neurons in opioid reward using conditional mu opioid receptor-knockout mice

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Opioid reward has traditionally been believed to occur through the activation of mu opioid receptors (MORs) in GABA neurons within the ventral tegmental area (VTA). However, recent findings have challenged this notion by revealing high MOR expression in GABA neurons outside the VTA and in other neuronal types such as glutamatergic neurons. Nevertheless, the functional significance of MORs in GABA versus glutamate neurons in opioid reward remains poorly understood. To address this gap, we employed Cre-LoxP techniques to generate conditional MOR-knockout (KO) mice, selectively deleting MORs from either GABA or VgluT2-positive glutamate neurons. Comparing these MOR-KO mice to wildtype littermates, we observed that MOR deletion from GABA neurons partially reduced heroin self-administration (SA), while deletion from glutamate neurons completely blocked heroin SA, indicating a more crucial role for glutamatergic MORs in opioid reward. Further investigation identified the paraventricular thalamus (PVT) as a critical site of MOR expression in VgluT2+ glutamate neurons. Using optogenetics in VGluT2-Cre mice, we demonstrated that activation of PVT glutamate neurons increased heroin SA and intake, while their inhibition had no significant effect on heroin SA. Additionally, optical real-time place preference revealed aversion with PVT glutamate neuron stimulation, suggesting that increased heroin SA could be a compensatory response in drug intake to counteract aversion produced by optical stimulation of PVT glutamate neurons. Future research will elucidate specific PVT glutamate pathways involved in opioid reward. These findings challenge and refine our understanding of cell type-specific mechanisms underlying opioid reward.

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