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# REWARDING EFFECTS OF OPIOIDERGIC PROJECTIONS FROM THE VENTRAL PALLIDUM TO SUBSTANTIA NIGRA

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Opioid addiction has reached epidemic levels recently, but the role of endogenous opioid circuits is still poorly understood. The rewarding effects of opioids are believed to be due to inhibition of tonic GABAergic inputs to midbrain dopamine neurons, releasing these neurons from inhibition and increasing dopamine release. The ventral pallidum (VP) is one of the strongest projections to the midbrain dopamine neurons and expresses the opioid peptide enkephalin at high levels. We hypothesized that stimulation of VP enkephalin projections to the substantia nigra pars compacta (SNc) would be rewarding and mediated by enkephalin. We used Penk-IRES-Cre mice, which express Cre recombinase exclusively on enkephalin neurons for optogenetic and chemogenetic manipulations in the VP. Cre-positive mice and littermate controls were injected either with a cre-dependent channelrhodopsin virus or with a Cre-dependent inhibitory chemogenetic actuator in the VP. We used optically-evoked real time place preference (RTTP) and intracranial self-stimulation (ICSS) to measure reward. For our chemogenetic experiments we used conditioned place aversion and operant sucrose self-administration as behavioral readouts. We found that enkephalin-positive VP-SNc projection bidirectionally controls reward. Stimulating Enk VP-SNc terminals was rewarding in both RTTP and ICSS. Chemogenetic inhibition of these same neurons resulted in a conditioned place aversion. Local infusion of GABA antagonists, mu and delta antagonists, and glutamate antagonists at a range of concentrations in the SNc did not block the light-induced preference in RTTP. We conclude that enkephalin-positive projections from the VP to the SNc bidirectionally control reward and aversion. Our preliminary results suggest that these effects might not be mediated by enkephalin, GABA or glutamate, although more experiments need to be done, including electrophysiology recordings. Understanding how endogenous opioid peptides modulate reward is crucial for understanding the mechanisms of opioid addiction.