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Transcriptional adaptations in the ventral pallidum following cocaine self-administration.

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Growing evidence suggests that the ventral pallidum (VP) is critical for drug intake and seeking behavior. Drug exposure is known to alter VP neuronal firing and neurotransmission but there is limited information on the molecular adaptations occurring in VP neurons following cocaine intake. To provide insight into cocaine-induced transcriptional alterations, we performed RNA-sequencing on VP of mice after 10 days of cocaine self-administration. We observed differential expression in 325 genes between cocaine and saline groups. Gene Ontology analysis of upregulated genes revealed significant changes in genes associated with dendrite and spine functions. The expression of the transcription factor Nr4a1 (involved in spine development) and its transcriptional targets Plk2 (important for synaptic and structural plasticity), showed a robust increase. Further assessment of the small GTPase Rap2 as well as actin dynamics supports spine remodeling after cocaine self-administration. To evaluate the role of Nr4a1 on cocaine intake, we overexpressed Nr4a1 prior to self-administration. Intake levels were not changed, however cocaine seeking was decreased. To understand this unexpected finding, we assessed Nr4a1 and Plk2 RNA levels in various VP projections retrogradely tagged with Cre. Fluorescent *in situ* hybridization revealed bidirectional changes: following cocaine self-administration, VP-Ventral Tegmental Area projection neurons display reduced, while VP-Lateral Habenula projection neurons exhibit increased Nr4a1 and Plk2 co-labeling. To understand the functional role of these changes, future experiments will manipulate Nr4a1 and Plk2 in a projection-specific manner during cocaine self-administration and relapse-like behavior. Altogether, our work can provide crucial information into the molecular substrates underlying cocaine addiction.