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

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Growing evidence suggests the ventral pallidum (VP) is critical for drug intake and seeking behavior. The VP is critical for the control of motivated behaviors. Repeated exposure to cocaine is known to alter VP neuronal firing and neurotransmission. Surprisingly, 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 the VP of mice that underwent 10 days of cocaine self-administration followed by twenty-four hours of abstinence. We observed differential gene expression in 363 genes between animals that self-administered cocaine and saline controls. Subsequent Gene Ontology analysis pointed toward alterations in dendrite- and spine-related genes. Searching for a common regulator for these sets of genes, we found that the expression of the transcription factor Nr4a1 showed a robust increase following cocaine self-administration. Further, we observed an increase in the Nr4a1 transcriptional target Plk2, a molecule important for synaptic and structural plasticity. Analysis of Plk2 molecular targets showed alterations in Actin and Rap2 dynamics after cocaine exposure, confirming alterations in dendritic and spine functions. Using fluorescent *in situ* hybridization, we determined that VP neuron projecting to the mediodorsal thalamus (MDT) showed increase Nr4a1 expression after cocaine intake. Subsequent overexpression of Nr4a1 in VP-MDT neurons increased cocaine seeking, confirming the role of our molecular target in drug seeking behavior. Altogether, our work can provide crucial information into the molecular adaptations occurring in VP neuron supporting cocaine self-administration and relapse-like behavior.