Accumbal E2F3a mediates cocaine behaviors via transcriptome-wide regulation of gene expression and alternative splicing

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Drug abuse is a chronic, multifaceted disorder that involves maladaptive decision making and is influenced by genetic and environmental factors. Long-lasting changes in neuronal gene expression in brain reward regions, including nucleus accumbens (NAc), contribute to persistent functional changes in the addicted brain. It is hypothesized that chronic drug exposure alters expression and function of upstream transcriptional regulators in NAc to regulate drug responses and the addicted phenotype. A recent large-scale genome-wide study from our group predicted E2F3 as a prominent upstream regulator of cocaine-induced changes in gene expression and alternative splicing. Our current study examined the expression of two isoforms of E2F3– E2F3a and E2F3b – in NAc after repeated cocaine administration. We took a multi-pronged approach and used viral-mediated isoform-specific gene manipulation, RNA-seq, ChIP-seq, advanced bioinformatics analyses, and animal behavior to determine how E2F3 mediates persistent transcriptional changes in brain reward circuitry following repeated cocaine exposure.

We show that the splice variant E2F3a, but not E2F3b, overexpression in NAc promotes cocaine locomotor and place preference behaviors. We powerfully complement these findings by showing E2F3a overexpression substantially recapitulates transcriptome-wide cocaine-induced gene expression profiles. Furthermore, we find that E2F3a overexpression recapitulates the effects of cocaine on alternative splicing events in the NAc. Finally, we validate direct binding of E2F3a at predicted target genes following cocaine exposure. Specifically, *Ptbp1*, *Tle2,* and *Fgfr1* appear to be regulated by directed E2F3a binding. These findings establish E2F3a as a transcriptional regulator of cocaine action in NAc, and suggest this splice variant as a novel target for future therapeutic intervention.