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Chromatin- and Activity-Mediated Alternative Splicing in Sucrose and Cocaine Reward

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Alternative splicing, the inclusion and exclusion of regions in the mature RNA transcript, represents a vital mechanism of dynamic gene regulation. In the brain, environmental stimuli regulate alternative splicing of specific mRNA transcripts. Defects in neuronal splicing are associated with neurological and psychiatric disorders. To identify common regulatory pathways of alternative splicing in brain, we analyzed activity-mediated regulation of genome-wide alternative splicing in three distinct studies. First, KCl stimulation of mouse primary cultured neurons regulated the inclusion of >1000 alternative exons common to five publicly available, independent datasets. We found that alternative exons were in genes that were not differentially expressed by KCl, and a divergence in functional changes after short and long KCl stimulation. Second, we found regulation of alternative splicing in mouse dorsolateral and dorsomedial striatum following sucrose self-administration. Third, we analyzed alternative splicing in dorsal and ventral striatum after cocaine self-administration. We validated cocaine-driven splicing events, including at Bin1, using quantitative radioactive PCR. In all cases, stimulus-dependent changes in gene expression and alternative splicing regulated distinct genes, with distinct functions. Finally, we discovered an association between alternative splicing and enrichment of histone post-translational modifications over activity-dependent exons. We find redistribution of H3K36me3 over activity-regulated exons, further implicating the epigenome in neuronal splicing. In sum, this study underscores that neurons respond to stimuli through unique regulation of transcriptional and post-transcriptional gene expression.