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Long non-coding RNAs form DNA:RNA hybrid structure, R-loops, that function as an epigenetic gene regulatory layer underlying substance use disorder-related behaviors.

Emotional experiences often drive behavioral responses that enable organisms adapt to their environment. These experiences induce the expression of specific gene, initiating transcriptional programs that underlie cellular, synaptic, and behavioral plasticity. Tight regulation of these gene expression program is therefore essential for adaptive responses to emotional stimuli. Conversely, dysregulation of these transcriptional program is implicated in maladaptive behaviors associated with neuropsychiatric disorders, including mood and substance use disorder (SUD). We recently demonstrated that long non-coding RNAs (lncRNAs) form DNA:RNA hybrid structure known as R-loops across the genome in the mouse nucleus accumbens. Genes associated with these R-loops are identified in the glutamatergic and dopaminergic signaling pathways, calcium signaling pathways, and synaptic plasticity-related genes and also genes identified in human SUD genome-wide association studies. We discovered that neuronal activity induces the formation of R-loop at the enhancer region of immediate early gene, *Npas4*, a gene we previously identified as a key regulator of drug reward-associated contextual memory. This R-loop is essential for linking distal enhancer to the proximal promoter, facilitating *Npas4* gene expression, and regulating cocaine reward-associated contextual memory. Together, these data identify R-loops as novel regulatory mechanism that translates emotional experience into gene expression and behavioral plasticity. In this presentation, we will discuss the functional mechanisms of R-loops in gene expression and behavior in response to emotional experiences.

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