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A Long Non-Coding eRNA Forms R-loops to Shape Emotional Experience-Induced Behavioral Adaptation

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Substance Use disorder (SUD) is a chronic, relapsing condition characterized by compulsive drug seeking behaviors and consumption despite adverse consequences. The enduring associations between the rewarding properties of drugs and environmental cues linked to drug use produce powerful triggers for relapse in abstinent. However, the underlying molecular mechanisms are not fully understood.

While protein-coding genes (messenger RNAs [mRNAs]) are important for the functional regulation of brain activity and are targets for many neuropsychiatric conditions, both human and rodent genomes encode a much larger number of long-non-coding RNAs (lncRNA) with crucial roles in gene expression. Despite their importance, the physiological and pathological functions and mechanisms of individual lncRNAs are only beginning to be explored.

In our research, we discovered the novel lncRNA expression produced from enhancer region of neuronal activity-dependent immediate early gene, Npas4, which we previously demonstrated a key role in the nucleus accumbens (NAc) in controlling the development of cocaine conditioned place preference (CPP) and cocaine self-administration (SA) behaviors. This lncRNA forms a DNA:RNA hybrid structure known as R-loop, a three-stranded nucleic acid structure composed of an RNA:DNA hybrid strand and a displaced DNA strand. Our research reveals, for the first time, that R-loops play a key role in the neuronal activity-dependent Npas4 mRNA expression by facilitating the formation of a 3D chromatin loop that connect enhancer and promoter, and that this mechanism is necessary for the development of cocaine CPP. These findings highlight the functional role of R-loops in gene expression in the brain and SUD-related behaviors.