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A long non-coding enhancer RNA regulates NPAS4 in the NAc to control drug reward-conditioned behavior

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Substance Use Disorders is a long-lasting behavioral disease characterized by compulsive drug seeking and consumption despite negative consequences to individuals. Precise regulation of gene expression is important for adaptive brain function, and transcriptional mechanisms contribute to maladaptive changes in brain function that contribute to neuropsychiatric symptoms produced by substance abuse.

Recent advanced sequencing identified that human and rodent genome encode a much larger number of long-non-coding RNAs (lncRNAs) compared to the protein-coding genes (mRNAs). Emerging evidence has demonstrated significant roles for lncRNAs in multiple processes of gene expression, but researchers are only beginning to explore the physiological and pathological functions of individual lncRNAs. To address this knowledge gap, we investigated a novel, non-annotated, lnc-enhancer RNA (lnc-eRNA) transcribed from the enhancer region of Npas4 (Npas4 eRNA).

We previously found that a cocaine reward learning procedure induces immediate early gene, transcription factor, NPAS4 expression in the nucleus accumbens (NAc) and that its expression is required for the acquisition of cocaine reward-associated behaviors. Here we show a novel, non-annotated, lnc-enhancer RNA (lnc-eRNA) transcribed from the enhancer region of Npas4 (Npas4 eRNA) is required and sufficient for Npas4 mRNA expression in the NAc, and that Npas4 eRNA in the NAc is necessary for cocaine reward-conditioned behaviors. Ongoing studies are examining the mechanisms by which Npas4 eRNA regulates the activity-dependent induction of Npas4 mRNA. Together our studies reveal a novel role for an lnc-eRNA in the development of maladaptive behaviors produced by addictive substances.