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Striatal transcriptome-wide profiling of hnRNP H RNA-binding targets via CLIP-seq in response to methamphetamine identifies *Oprk1* as a potential translational target underlying reduced behavior in *Hnrnph1* mutant mice

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We previously identified *Hnrnph1* (heterogeneous nuclear ribonucleoprotein H1) as a quantitative trait gene underlying reduced methamphetamine (**MA**) behavioral sensitivity. Mice with a heterozygous frameshift deletion in the first coding exon of *Hnrnph1* (*Hnrph1+/-*) showed reduced sensitivity to the stimulant, rewarding, reinforcing effect of MA and a decrease in MA-induced dopamine release. The deletion is in one of the RNA binding domains of *Hnrnph1*. The RNA binding targets of hnRNP H in the brain and its *in vivo* function are largely unknown. My first-author preprint (https://doi.org/10.1101/717728; in minor revision, *Journal of Neuroscience*) suggests a drug-induced cell biological mechanism underlying deficits in MA neurobehavioral responding. To gain mechanistic insight, we examined mRNA binding targets of hnRNP H via cross-linking immunoprecipitation coupled with high-throughput sequencing (**CLIP-seq**) in striatal tissue at baseline and following MA (2 mg/kg, i.p.). The predominant binding regions for hnRNP H were intronic, supporting its role in splicing. MA administration decreased hnRNP H binding to RNA targets. A top target was *Oprk1* which codes for the Gi/Go-coupled kappa opioid receptor (KOR). KOR is located presynaptically on dopaminergic neurons where activation inhibits dopamine release. hnRNP H binding to the 5'UTR of Oprk1 was decreased in response to MA. Our working hypothesis is that hnRNP H represses Oprk1 translation via 5'UTR binding. MA administration de-represses translation of Oprk1 by decreasing binding to hnRNP H. This rapid adaptive cellular response serves to counteract the surge in MA-induced dopamine release and restore cellular function to baseline.