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Alternative splicing in a mouse model of *Oprm1* A118G

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There is growing evidence that mRNA alternative splicing is altered by drugs of abuse and contributes to addiction-like behavior. This is understudied in the context of opioids, although the gene encoding the mu opioid receptor, OPRM1, is extensively spliced. The typical protein is a 7-transmembrane domain GPCR, but several alternative transcripts produce truncated 6TM proteins, which have reduced or lost affinity for opioid ligands. These are produced via usage of an alternative promoter and first exon, E11, upstream of the normal first exon, E1, which is excluded. Preliminary evidence suggests that 6TM isoform expression inversely correlates with opioid sensitivity in mice and is preferentially upregulated after opioid exposure, suggesting a role in addiction and tolerance. GWAS have identified the single nucleotide polymorphism *OPRM1* A118G, located in E1, as a likely risk locus for opioid use disorder. Mice with the equivalent variant, A112G, display elevated intravenous self-administration of heroin and oxycodone. G/G mice also have reduced mRNA containing E1, reduced binding of radiolabeled opioid ligands, and reduced synaptic response to opioids in the hippocampus and VTA. The mechanism of altered mRNA expression has never been identified, and alternative isoforms have never been quantified. We hypothesize that G/G mice have reduced 7TM isoform expression and elevated 6TM isoform expression, mediating the partial loss-of-function phenotype. For the first time, we will quantify isoform specific *Oprm1* expression in reward-related brain regions of A/A and G/G mice exposed to experimenter-administered morphine or saline (n = 4 male, 4 female per genotype) using Nanopore long-read sequencing.