

**Aberrant alternative pre-mRNA splicing of the mu opioid receptor gene, *OPRM1*, in the medial prefrontal cortex of human heroin abusers and heroin self-administering rats**

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Heroin, a mu agonist, acts through the mu opioid receptor. The mu opioid receptor gene, *OPRM1*, undergoes extensive alternative splicing, creating an array of splice variants that are conserved from rodent to humans. Increasing evidence suggests that these *OPRM1* splice variants are pharmacologically important in mediating various actions of mu opioids, including analgesia, tolerance, physical dependence, rewarding behavior, as well as addiction. However, it remains largely unknown how expression of the *OPRM1* splice variants impact on heroin addiction in humans and animals. In the present study, we examine expression of the *OPRM1* splice variant mRNAs in the medial prefrontal cortex (mPFC), one of the major brain regions involved reward, decision-making and drug-seeking behaviors, of human heroin abusers and rats that developed stable heroin seeking behavior using the intravenous heroin self-administration (SA) model. The results show varied expression levels among the *OPRM1* splice variants in human postmortem tissues, which is similar to those in the rats, further illustrating conservation of *OPRM1* alternative splicing from rodent to humans. Moreover, the expressions of several *OPRM1* splice variant mRNAs were dysregulated in postmortem mPFCs from heroin abusers compared to the control subjects. Similar patterns were observed in the rat heroin SA model. Together, these results suggest the involvement of the *OPRM1* splice variants in heroin addiction and the usefulness of the rat heroin SA model.

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