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Targeting Exon 7-associated 7TM C-Terminal Variants of the Mu Opioid Receptor Gene for Mitigating Adverse Effects of Mu Opioids Without Altering Analgesia in Pain Management

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The single-copy gene (*OPRM1*) encoding the mu opioid receptor (MOR) undergoes extensive alternative splicing, generating multiple splice variants. One set of *OPRM1* variants, exon 7-associated full-length 7 transmembrane (TM) C-terminal splice variants (E7 variants), contain a unique intracellular C-terminal tail with 30 amino acids encoded by E7 that are highly conserved from rodents, primates to humans. E7 variants are abundantly expressed in the central nervous system with distinct distributions among brain regions. Cumulative evidence has indicated that these E7 variants play a crucial role in mediating various adverse effects associated with clinically used mu opioids, such as tolerance, reward, and respiratory depression. For example, truncating E7-enocded C-terminal tails in mice (mE7M-B6) attenuated morphine tolerance and reward, while not affecting analgesia. The current studies further establish the role of E7 variants in mediating mu opioid-induced tolerance, reward, and respiratory depression in naïve mice and mE7M-B6 by using antisense oligos (ASOs) and a newly developed rabbit monoclonal antibody (RabmAb) that target E7 sequences. Intracerebroventricular administration of either the ASO or RabmAb attenuated morphine tolerance measured by radiant-heat tail-flick assay and reward measured by conditioned place preference (CPP) in mice. Additionally, we generated a new mouse model (mMOR-1O-KI) in which only a single E7 variant, mMOR-1O, is expressed to investigate the *in vivo* functions of mMOR-1O. The results showed that mMOR-1O-KI mice had enhanced morphine tolerance and reward (CPP), complementing those the results from mE7M-B6 mice and further supporting the role of E7 variants in mediating these effects. Furthermore, fentanyl-induced tolerance, reward and respiratory depression measured by whole body plethysmography were significantly reduced in mE7M-B6 mice. Together, these studies indicate that targeting E7 variants presents a promising approach to mitigate tolerance, reward, and respiratory depression associated with clinically used mu opioids, while preserving their analgesic properties mediated by other *Oprm1* 7TM variants.

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