Alternatively Spliced Variants of the Mu Opioid Receptor Gene, *Oprm1*, Differentially Mediate Opioid-Induced Respiratory Depression in Rats

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Opioid overdose deaths have skyrocketed by 3.5x in the last decade, mainly due to "opioid-induced respiratory depression (OIRD)." Understanding the mechanisms underpinning this is essential towards prevention and the development of new effective interventions. Mu opioid actions, including analgesia, tolerance, addiction and OIRD, are primarily mediated through mu opioid receptors (MOR). The single-copy MOR gene, *Oprm1*, undergoes extensive alternative splicing to generate two classes of MOR splice variants: Exon 1- (E1) and Exon 11- (E11) associated variants. The functional relevance of these splice variants has been demonstrated in mediating the actions of various mu opioids, including analgesia, tolerance, physical dependence, and reward. However, it remains unknown how the two sets of *Oprm1* splice variants influence OIRD. To address this question, we used two *Oprm1* gene targeted rat models, in which E1- or E11-associated variants are floxed with loxPs and can be conditionally disrupted by Cre-loxP recombination. We measured OIRD induced by morphine and fentanyl in these rat models under awake and unrestricted conditions using Whole-Body Plethysmography (WBP) technology that can define specific changes in respiration from opioids. The results demonstrated that E1- and E11-associated variants differentially influence OIRD, with varied responses from morphine and fentanyl administrations, as well as between male and female rats. Additionally, OIRD responses in rats differed from those in mice, suggesting species differences in OIRD. Together, this study not only provides a deeper understanding of the unique role of E1- and E11-associated variants on OIRD, but also enables the development of potential therapeutic strategies to reduce unnecessary opioid-related deaths.

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