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"Alternatively Spliced Variants of the Mu Opioid Receptor Gene, *Oprm1*, Differentially Regulate Opioid-Induced Respiratory Depression in Key Brainstem Respiratory Centers"

By

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Tuesday, December 2nd, 2025
Medical Science Building, B-619
10:30 A.M.

Join Zoom presentation

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Meeting ID: 967 1676 0731
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ABSTRACT

Opioids, among the oldest known medicines, remain essential for pain relief yet drive a growing global crisis. Opioid-induced respiratory depression (OIRD) is the leading cause of overdose deaths, demanding urgent research to develop safer treatments and targeted rescue strategies. The mu opioid receptor gene, *Oprm1*, undergoes extensive alternative splicing to generate two major classes of variants: Exon 1-associated full-length 7-transmembrane (TM) C-terminal variants (E1-variants) and Exon 11-associated truncated 6TM N-terminal variants (E11-variants). These variants have distinct functional roles in mediating opioid actions, including analgesia, tolerance, dependence, and reward. However, the precise ways in which E1- and E11-variants shape OIRD are still unknown. To address this question, we used two sets of *Oprm1* gene-targeted rat models, in which E1- or E11-associated variants are floxed with loxP sites ($rE1^{f/f}$ and $rE11^{f/f}$) and their corresponding knockout models by Cre-loxP recombination ($rE1^{d/d}$ and $rE11^{d/d}$) to measure OIRD using whole body plethysmography (WBP) technology. Our results demonstrated that E1- and E11-associated variants differentially influence OIRD, with drug, dose, and sex differences from three opioids (fentanyl, morphine, and buprenorphine). We then focused on unraveling the role of E1-variants and E11-variants in two key brainstem regions, the preBötzinger complex (preBötC) and parabrachial nucleus (PBN), on OIRD. Here, E1- or E11-variants in the preBötC, PBN, or both were knocked out in $rE1^{f/f}$ and $rE11^{f/f}$ rats by using AAV-Cre microinjections. Our data indicate that the E1-variants and E11-variants differentially regulate breathing patterns in region-, mu opioid-, and sex-specific manners, providing novel insights into the mechanisms underlying the role of E1-variants and E11-variants on OIRD. Lastly, we mapped *Oprm1* and variant expression in the preBötC and PBN through spatial and transcriptomic approaches. The results revealed that both E1- and E11-variants are predominantly localized to neurons. *Oprm1* variants are also expressed in astrocytes and microglia, suggesting that glial cells may contribute to OIRD alongside neuronal pathways. Taken together, this work provides the first comprehensive study linking specific opioids, *Oprm1* variants, brain regions, and cell types to respiratory control, providing novel insights into the mechanisms underlying OIRD, and laying the groundwork for developing new strategies to prevent opioid overdose deaths.