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Mu opioid-induced biased signaling through mu opioid receptor seven transmembrane full-length C-terminal splice variants

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Background: The mainstays of pain management for moderate and severe pain remain to be mu analgesics that exhibit many side-effects associated with traditional opiates. A single-copy mu opioid receptor (*OPRM1*) gene generates a vast array of mu opioid receptor splice variants through extensive alternative splicing that is conserved from rodent to human. One set of these variants are 7 transmembrane (TM) full-length C-terminal splice variants that play important role on mu opioid pharmacology, which has been demonstrated using C-terminal truncation mouse models.

Rationale/Significance: Further investigating the role of the 7TM full-length C-terminal variants in mu opioid-induced biased signaling will advance our understanding of complex mu opioid pharmacology.

Hypothesis: Mu agonists can produce differential biased signaling through mu opioid receptor 7TM full-length C-terminal splice variants.

Result: Various 7TM full-length C-terminal variants displayed significant differences in mu agonist-induced G protein coupling measured by [³⁵S]γGTPS binding and in receptor β-arrestin2 binding measured by β-arrestin2 recruitment PathHunter assay (DiscoverX) in the same CHO cells stably expressing individual C-terminal variants. Biased factors calculated by Black and Leff model from both [³⁵S]γGTPS binding and PathHunter assay varied markedly among different variants and among different mu agonists. Great β-arrestin2 bias with exon 7-associated C-terminal variants, particularly mMOR-1O, for almost all the mu agonists.

Discussion: Our results suggest that 7TM full-length C-terminal variants have significant impact on mu agonist-induced biased signaling and provide new insights on complex mu opioid actions.