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Spatial mapping of human OPRM1 exon O-associated splice variant, hMOR-1O, in the brain by BaseScope: Implications for human opioid pharmacology

The human OPRM1 gene undergoes extensive alternative splicing, yielding multiple splice variants. One variant, hMOR-1O, is an exon O (EO)–associated homolog of rodent Oprm1 E7 variants. It retains the canonical 7TM receptor structure encoded by exons 1-3 but carries a unique 30-amino-acid intracellular C terminal tail encoded by exon O, highly conserved across rodent, nonhuman primate, and human lineages. In mice, E7 variants have been indicated to mediate mu opioid–induced adverse effects, including tolerance, reward, and respiratory depression, and are widely expressed in central and peripheral nervous systems. However, the distribution and neuronal expression of hMOR-1O in humans remain unclear. We developed a BaseScope assay with an E3/EO probe targeting hMOR-1O and an E3/E4 probe targeting canonical hMOR-1, combined with NeuN immunohistochemistry, to map neuronal expression of hMOR-1O and hMOR-1 transcripts in several human and rhesus monkey brain regions, including prefrontal cortex, hippocampus, and hypothalamus. hMOR-1O mRNA was detectable in NeuN-positive neurons across all examined regions, mirroring the widespread neuronal distribution of hMOR-1. The fraction of NeuN-positive cells expressing hMOR-1O was comparable to that expressing hMOR-1, though absolute hMOR-1O transcript levels were generally lower than those of hMOR-1. Similar patterns were observed in the hippocampus and hypothalamus of mice and rhesus monkeys. These data demonstrate that the human brain expresses hMOR-1O in a broad neuronal distribution similar to hMOR-1, with lower transcript levels, suggesting a potential role for hMOR-1O in mu opioid–related adverse effects and warranting further functional investigation. Supported in part by grants from NIH (DA060222 and DA059061), Rutgers Addiction Research Center, Brain Health Institute, Department of Anesthesiology, Rutgers New Jersey Medical School.

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