MOPr-DOPr heteromer: The meaning and possibility as novel therapeutic target for pain control

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Many studies suggest opioid receptor (OPr) dimerization modulates the pharmacological properties of opiates. Specifically, heteromerization between OPr types has been reported to lead to changes in intracellular signaling. Thus, ligands targeting heteromers are expected to be novel therapeutic targets with reduced side effects. The heteromers of mu (MOPr) and delta (DOPr) are detected in brain regions involved in pain processing. By high-through-put screening, CYM51010 was identified as a MOPr-DOPr-biased ligand. Furthermore, CYM51010 exhibits antinociceptive properties similar to that of morphine with lesser antinociceptive tolerance as compared to morphine. Studies exploring the *in vivo* regulation of MOPr-DOPr heteromers, showed chronic morphine administration leads to an upregulation of these heteromers in select brain regions. Exploration of mechanisms underlying this phenomenon led us to the G protein-coupled receptor chaperone, RTP4, that is induced by chronic morphine and facilitates the heteromerization of MOPr and DOPr. In this presentation, I will present the identification and characterization of CYM51010 and the role of RTP4 in heteromer regulation that could serve as a scaffold for the development of novel therapeutic drugs with reduced adverse effects, and hence may take place of the conventional clinical opioids.