G-PROTEIN-COUPLED RECEPTORS

It takes two…

Long awaited proof that G-protein-coupled receptors (GPCRs) form functional heterodimers *in vivo* has finally been found. Jennifer Whistler and colleagues, writing in *Proceedings of the National Academy of Sciences*, report tissue-selective expression of an opioid heterodimer that is selectively targeted by an analgesic compound. If this concept extends to other GPCR families, heterodimers could represent a large pool of unprecedented drug targets.

Although many *in vitro* studies have hinted at the importance of dimerization, conclusive proof of a physiological role for GPCR heterodimers has been elusive. Whistler and colleagues proposed that a ligand that selectively targeted an opioid heterodimer would provide this proof. Furthermore, as many of the side effects associated with opiate analgesics are eliminated if the drug is administered directly into the spinal cord, the ability to selectively target opioid heterodimers in the spine could be beneficial.

Knowing that δ- and κ-opioid peptide receptors (DOP-R and KOP-R, respectively) coexist in spinal neurons, and that spinal-cord-selective activity of a bivalent antagonist specific for DOP/KOP-R has recently been reported, the authors proposed that DOP/KOP-R heterodimers might represent a target for the development of a spinal-selective analgesic.

Their investigation focused on an analgesic compound, 6′-guanidinonaltrindole (6′-GNTI), which, although supposedly a KOP-R-selective agonist, was shown to exhibit variable agonistic activity in different tissues. This led the authors to speculate that the target for 6′-GNTI was tissue-specific and could be an opioid receptor heterodimer. To study this hypothesis they used cells stably transfected with murine opioid receptors (MOP-Rs), DOP-Rs and KOP-Rs either alone or coexpressed and measured opioid receptor signalling.

The most potent agonism was observed in cells that coexpress KOP-R and DOP-R, and could not be explained by synergistic activation. Addition of subtype-selective antagonists confirmed that the activity of 6′-GNTI requires both KOP-R and DOP-R: antagonism of either subtype abolished 6′-GNTI-mediated signalling. Because the affinities of the antagonists for the individual receptors were different to those when heterodimerized, the authors proposed that heterodimerization creates a unique signalling complex — a 'landing pad' for 6′-GNTI — and might also cause a change in conformation that alters ligand affinity for each receptor.

Following on from their *in vitro* data, the authors then went on to show that 6′-GNTI elicited analgesia when administered directly into the spinal cord, but almost no analgesia when administered directly to the brain. Moreover, this spinal-selective analgesic effect was blocked by a bivalent selective-DOP/KOP-R antagonist, confirming that the heterodimer is a functional target for analgesia *in vivo*.

The proof that opioid heterodimers are functionally relevant *in vivo* makes it reasonable to extrapolate that the same could be true for other GPCR families. The authors speculate that so-called 'orphan' GPCRs might actually be dimerization partners for GPCRs with known ligands, which serve to increase the complexity, and therefore subtlety, of GPCR signalling. This intriguing possibility means that the number of feasible permutations of GPCR heterodimers and their potential modes of activation provides many more avenues for refined therapeutic intervention. That many of these complexes are selectively expressed also bodes well for the future development of tissue- and subtype-selective GPCR-targeted drugs.

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References and links

ORIGINAL RESEARCH PAPER Waldhoer, M. *et al.* A heterodimer-selective agonist shows *in vivo* relevance of G protein-coupled receptor dimers. *Proc. Natl Acad. Sci. USA* **102**, 9050–9055 (2005)