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How opioid drugs bind to receptors

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Abstract

The search for safe, non-addictive versions of morphine and other opioid drugs has just received a boost with the solving of the crystal structures of the receptors to which the drugs bind.

Opioid drugs such as morphine and codeine are powerful painkillers, but an assortment of adverse side effects limits their effective medical use. These drugs can also produce pronounced euphoria, which has led to the recreational use of common prescription painkillers. Addiction to prescription opioids is currently one of the most severe forms of drug abuse[1], a fact that raises significant public-health concerns and highlights a pressing need for the development of safer painkillers. In this issue, four papers[2–5] report crystal structures that provide the first direct evidence for the binding mode of opioids to their receptors. This information will be invaluable for research aimed at finding opioid drugs that lack the adverse side effects.

Opioid receptors (ORs) are members of the superfamily of G-protein-coupled receptors (GPCRs). The traditional model of OR signalling proposes that the binding of a ligand molecule (an opioid) to a receptor activates an associated G protein, which, in turn, triggers a biological response. Widely distributed in the brain and in the peripheral nervous system, the four types of OR are μ-OR, δ-OR, κ-OR and the nociceptin/orphanin FQ peptide receptor. These receptors represent prominent targets not only for painkillers, but also for antidepressants, anti-addiction medications and anti-anxiety drugs.

The papers in this issue[2–5] present the long-awaited, high-resolution crystal structures of all four ORs in ligand-bound conformations. The ligands are all antagonists (receptor blockers), which means that the structures depict inactive states of the receptors. These crystal structures are the latest to have been obtained using revolutionary technologies — including the replacement of part of the receptors with another protein, such as T4 lysozyme[6,7], to facilitate receptor crystallization — that have enabled successful structural determination of several GPCRs. Such proteins were once intractable to crystallography.

The four OR structures reveal several evolutionarily conserved ligand–receptor interactions in the receptors' binding pockets, which are contained within the seven transmembrane helices (designated TM1–7) of the receptors. For instance, several amino-acid residues at the same positions in TM3, TM6 and TM7 form interactions with the chemical moieties of ligands that are responsible for opioid efficacy — the 'message' region of the ligands. By contrast, the chemical moieties responsible for opioid selectivity — the 'address' region — occupy one of two different areas of the binding pocket, depending on the type of opioid. Specifically, the addresses of classical opioids, which contain the 'morphinan' chemical

structure, interact with TM6 and/or TM7, whereas the corresponding regions of the other opioids studied are positioned between TM2 and TM3 of the receptor (Fig. 1), forming inter actions mostly with those helices, but also with TM7. Accordingly, Wu and colleagues suggest[3] that the message–address hypothesis of opioid binding may not apply uniformly to all opioid ligands.

The transmembrane structures of the four ORs are very similar to each other, as expected given that the amino-acid sequences of these structures are also very similar (homologous, to use the jargon). More surprisingly, the structures of non-homologous loop regions, such as the long, extracellular loop region ECL2, are also very alike. Notably, the ECL2 structure of the ORs is similar to that[8] of CXCR4 — another GPCR that, like the ORs, binds both peptides and small molecules. This shared, 'β-hairpin' loop structure creates a wide opening that allows ligands unobstructed access to the primary binding pocket within the transmembrane region. Manglik *et al.* suggest[4] that this might explain why the effects of most opioid drugs are highly potent yet rapidly reversible.

Analysis of the OR crystal structures also reveals an unexpected outward displacement of the extracellular half of TM1 away from the long axis of κ-OR (ref. 3), compared with the other opioid receptors[2,4,5] and CXCR4 (ref. 8). However, as previously noted[9,10] in the case of another GPCR — the β1-adrenergic receptor — different conformations of TM1 (and TM6) can be identified in inactive structures as a result of different crystal-packing interactions and/or crystallization conditions. In other words, the unusual conformation of TM1 in κ-OR may simply be one of many conformations that could have been adopted by the helix. This is an important point, as it reflects the intrinsic dynamic nature of GPCRs. Moreover, it reminds us that crystal structures of GPCRs are single, static snapshots of receptors stripped of their natural lipid environment, and might therefore offer limited mechanistic insight.

Evidence suggests[11] that the most addictive opioids promote OR interactions with their G proteins more strongly than with arrestin, another cellular signalling protein. To develop drugs that retain the therapeutic action of opioids but not the unwanted side effects, it is therefore crucial to understand the specific receptor conformations that opioids stabilize to selectively activate signalling pathways. This important aspect of ligand binding to ORs is not captured by the recent crystal structures, and should be the subject of future research.

There is also compelling evidence[12,13] that different types of OR associate with each other, or with other GPCR subtypes, to form dimers and oligomers, and that this changes the signalling properties of the ORs, thereby adding an additional level of complexity to an already multi-faceted problem. Manglik and colleagues' structure[4] of the μ-OR shows tightly associated pairs of receptor molecules, held together predominantly by highly complementary interactions involving TM5 and TM6. The researchers speculate that this pairing might regulate the signalling of the receptor. A similar inter action was noted[8] in the structure of CXCR4, but is not found in the other OR structures[2,3,5].

By contrast, the κ-OR structure shows a dimeric arrangement involving interactions of TM1, TM2 and helix 8 (H8), which is similar to the alternative, less compact crystal packing seen in the μ-OR structure. The proposed roles of the TM5–TM6 and TM1–TM2–H8 interfaces are only two of several working hypotheses of functionally relevant receptor–receptor interactions that need to be addressed to enable investigators to examine the role of dimerization (or oligomerization) in the signalling of ORs. The quest for functionally relevant oligomerization interfaces therefore continues.

These crystal structures[2–5] of inactive ORs will contribute crucial information to a broad range of therapeutic areas, including those focused on pain, addiction and mental disorders.

Future crystal structures of active ORs in complex with different signalling proteins could provide necessary — although not sufficient — information for elucidating the mechanisms underlying receptor function. A complete understanding will also require the integration of experimental and computational strategies that allow the study of receptors in a natural lipid environment — necessary to obtain rigorous mechanistic insight, at the molecular level, into the ligand-induced conformation selection, spatio-temporal organization and dynamics of OR complexes. The challenge will then be to translate that knowledge from bench to bedside, by fine-tuning OR signalling towards therapeutic pathways, and away from those that mediate adverse side effects.

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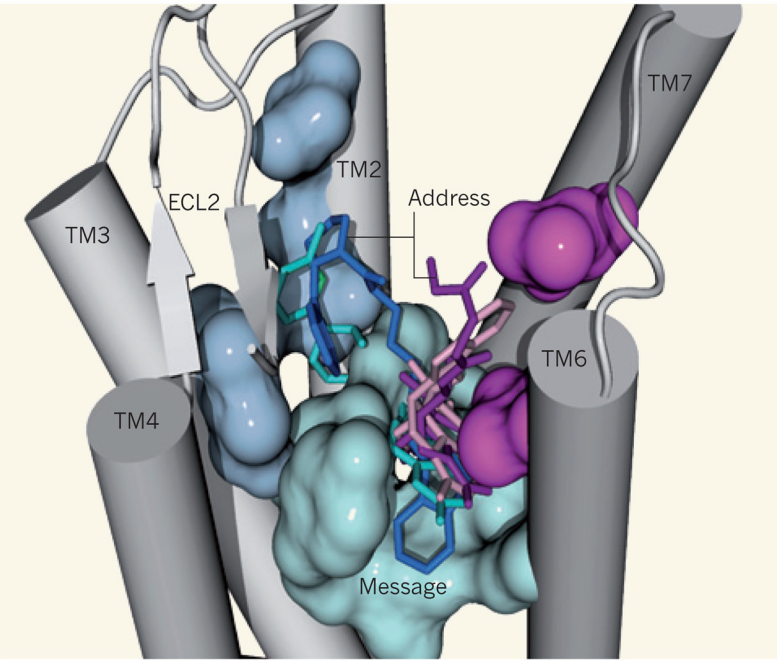

Figure 1. Binding mode of opioids at their receptors

The structures of the four types of opioid receptor, each in complex with a different opioid antagonist, have been solved[2–5]. A side view of one of the structures — that of the nociceptin/orphanin FQ peptide (NOP) receptor — is depicted to show features shared by all four receptor types. Only five of the seven transmembrane helices (TM1–7) are shown (grey cylinders). ECL2 is a β-hairpin loop region; the arrows represent β-sheets. The four antagonists used in the studies are depicted as stick representations in the NOP receptor's binding pocket. The cyan surface indicates the amino-acid residues from TM3, TM6 and TM7 that interact with the ligands' 'message' regions, responsible for a ligand's efficacy. The magenta surfaces indicate the residues from TM6 and/or TM7 that interact with the 'address' region — responsible for opioid selectivity — of classical ligands, which contain the 'morphinan' chemical structure. The light-blue surfaces represent residues from TM2 and TM3 that interact with the address region of non-classical opioids.