RESEARCH HIGHLIGHT

G_z and β-arrestin 1 signaling in the μ-opioid receptor

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In a recent study published in *Cell Research*, Zhang et al. reported cryo-electron microscopy (cryo-EM) structures of μ-opioid receptor (MOR) in complex with the nonconventional G protein G_z and β-arrestin 1, highlighting how transmembrane helix 1 (TM1) mediates biased transducer signaling. The newly identified TM1-fusion pocket brings new insights into the MOR activation mechanisms and paves the way for the discovery of novel analgesics with attenuated side effects.

The μ-opioid receptor (MOR) is one of the most intensely studied G protein-coupled receptors (GPCRs), owing to its central role in both mediating the analgesic actions of opioids and fueling the ongoing opioid crisis.[1] For decades, neuroscientists, biochemists, and pharmacologists have sought to understand how this one receptor can generate such diverse biological outcomes — ranging from pain relief or euphoria to tolerance, respiratory depression, and addiction.[2] MOR signals by intracellular transducers including G proteins, G protein-coupled receptor kinases (GRKs), β-arrestins depending on the ligand and physiological condition (Fig. 1a). The strategy of creating G protein-biased opioids has been suggested as an approach to create safer analgesics since arrestin activation is believed to be responsible, in part, for some adverse effects.[3] While numerous structures of MOR bound to G_i and ligands provide valuable insights into the receptor activation mechanisms, the structural features responsible for coupling with other transducers remain unknown.[4,5]

The study by Zhang and colleagues offers the most complete structural comparison of MOR activation states to date.[6] Achieving structural stabilization of these complexes required engineering strategies, including the use of fusion protein constructs. The resulting high-resolution maps reveal detailed interfaces between the receptor and its transducers, allowing the authors to compare three activation states side by side: MOR–G_i, MOR–G_z, and MOR–β-arrestin 1 (βarr1) (Fig. 1b). These structural comparisons revealed that although the overall receptor architecture remains similar across complexes, each transducer imposes subtle but meaningful differences in how the intracellular face of MOR rearranges. Among these divergences, one stood out prominently: the conformation and position of transmembrane helix 1 (TM1).

TM1 is located at the periphery of the seven-transmembrane helical bundle that defines all GPCRs. Historically, TM1 has not received attention related to receptor–effector coupling. Classical models emphasized changes in helices TM3, TM5, TM6, and TM7 during activation.[7] The new findings reveal that TM1 undergoes ligand- and transducer-dependent shifts. When MOR binds a G protein (G_i or G_z), TM1 swings outward, away from the receptor core. This outward displacement helps MOR form a broader hydrophobic cavity that accommodates G protein α-subunits. The expanded pocket allows the G protein C-terminal α5 helix to insert deeply, stabilizing the active state. When MOR binds βarr1, TM1 shifts inward, returning toward the helical bundle. This inward movement brings TM1 into closer contact with TM2 and TM7. The new interactions create a compact interface that is incompatible with G protein binding but favorable for arrestin engagement. Through these movements, TM1 acts as a gating element — a conformational switch that biases MOR toward either a G protein-favored configuration or an arrestin-favored one. This mechanism had not been recognized in previous structural works.

Further analysis revealed an internal region shaped by the relative positioning of TM1, TM2, and TM7, which the authors name the "TM1-fusion pocket". This pocket exhibits distinct geometries in each transducer-bound structure. In G protein complexes, the pocket is more open and allows structural flexibility at the cytoplasmic face. In the β-arrestin complex, the pocket tightens, effectively "locking" the receptor in an arrestin-compatible conformation. Molecular dynamics simulations reinforced this model by showing that TM1 has inherently high mobility and that its thermodynamic landscape changes depending on which ligand and transducer are bound. These dynamic features allow MOR to sample multiple signaling-competent conformations — providing the molecular basis for signaling plasticity. To confirm that TM1 indeed governs signaling, the researchers mutated key residues around the TM1-fusion pocket. The data show that altering TM1 alone was sufficient to shift the receptor's signaling bias. This functional evidence provides further validation that TM1 is a central regulator — not a peripheral bystander — in determining MOR transducer selectivity.

Perhaps the most far-reaching outcome of this work is the identification of a new structural target for rational drug design. The TM1-fusion pocket behaves like an allosteric switchboard that governs pathway selection. Small molecules or peptides designed to stabilize specific TM1 conformations could in principle bias MOR toward G protein signaling — promoting analgesia — while avoiding arrestin-dependent effects associated with respiratory depression and tolerance. Some opioids are shown to have higher affinity to G_z among $G_{i/o}$ family.[8] The discovery that G_z and G_i structures differ significantly expands our understanding of G protein subtype specificity.

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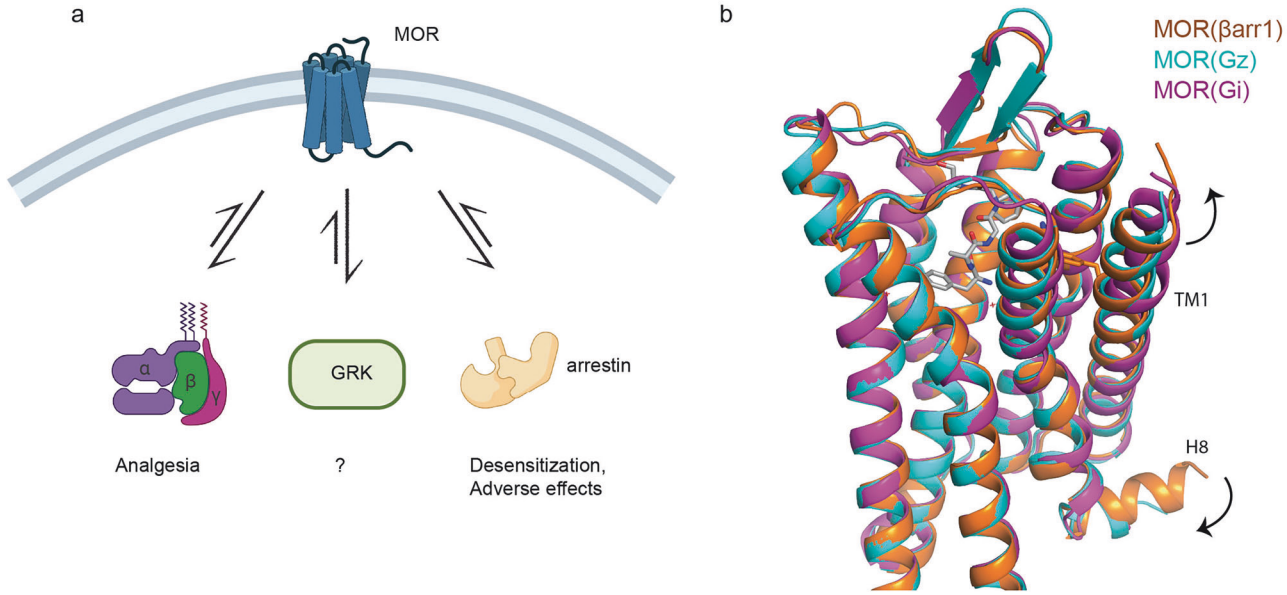

Fig. 1 Structural alignment illustrates the transducer specificity of MOR. a Signaling diversity of MOR mediated by various transducers. **b** Structural superimposition of MOR bound to βarr1, G_z and G_i (PDB: 6DDF). Arrows indicate the movement of TM1 and helix 8. H8, helix 8.

Taken together, by revealing that TM1 acts as a dynamic allosteric determinant of signaling bias, the authors provide a unifying mechanistic explanation for MOR's remarkable functional diversity. Beyond its relevance for opioid pharmacology, this work also broadens the conceptual toolkit for GPCR biology: it underscores that peripheral helices — often considered secondary players — can exert profound control over receptor output.

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COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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