Allosteric GPCR Pharmacology

The Allosteric Nature ofGPCRs

Allosteric Modulation

Indirect allosteric modulation describes the interactions between an orthosteric ligand and other functionally-linked binding sites on the same receptor. Allosteric modulatory sites can be grouped into five categories, depending on the location of the orthosteric site(s) on the inactive-state conformation of the GPCR. This image below shows the main interfaces that have been implicated in structural biology studies, mapped onto the dimeric structure of the mGlu5 receptor.

Microswitches Governing The Allosteric Transition (GPCR Activation)

The allosteric transition is governed by a series of conserved intermolecular interactions (or microswitches), between orthosteric and allosteric binding sites. Key microswitches in class A GPCRs include the Gly-X-Pro loop, the P-loop, and the ERY motif. The figure shows these common microswitches in the class A GPCR allosteric transition, mapped onto the inactive state (white, PDB: 1F88) and active state (blue, PDB: 4NQ2).

Conformational Mechanisms of Biased Agonism

There are many potential advantages of allosteric modulators as therapeutic drugs in comparison to classic orthosteric ligands:

- The lower degree of amino acid conservation within allosteric sites relative to the orthosteric sites means there is greater potential for biased activation with lower off-target effects.
- The effect of allosteric drugs is governed by the degree of cooperativity between orthosteric and allosteric sites, which permits greater control of on-target dose-related side effects. This potentially allows an allosteric modulator to be more efficacious at its GPCR target by opening up opportunities to exploit therapeutic windows that may have been too narrow for classic orthosteric medicines alone.
- "Pure" PAMs or NAMs are quiescent in the absence of orthosteric endogenous agonist, exerting their effect only where and when the endogenous agonist is released. This means that tissue-specific conditions can be exploited to generate ligand-gated ion channels in a given region as a consequence of disease. For example, in a tissue with high endothelial jumps, a receptor will be differentially sensitive to the allosteric drug effects than the same receptor in other tissues in the body, reducing "off-tissue" (i.e. non-target) effects.
- Allosteric ligands may cause endogenous agonists to exhibit biased signaling, providing another approach to selectively target desired pathways.

Impact of Differential Architecture on Allosteric Signaling

GPCRs have been shown to oligomerize, adding an extra dimension to allosteric modifications. With studies highlighting the potential for allosteric interactions between binding sites on GPCRs within dimeric or higher order oligomeric forms. Docks in the diagram above, show the main interfaces that have been implicated in structural biology studies, mapped onto the dimeric structure of the mGlu5 receptor.

Diversity in the Binding Sites of Synthetic Allosteric Modulators across GPCR Classes

Class A GPCR allosteric modulators include the class A (M_2 mAChR, PDB: 4MQT), class B (GCGR, PDB: 5EE7), and class C (mGlu5, PDB: 4OO9) GPCRs. As heterotrimeric G proteins. This is termed the 'allosteric transition'. This poster highlights some of the key insights into allosteric mechanisms of GPCR biology.

The Key Facets of GPCR Allostery

A. Positive allosteric modulators (PAMs), negative allosteric modulators (NAMs), and neutral allosteric ligands (NALs): Allosteric modulators are characterized through different modes of behavior: PAMs, NAMs or NALs.

B. "Probe" dependence is another unique pharmacological characteristic of allosteric modulators where the magnitude and direction of the allosteric effect can change on the orthosteric ligand.

C. Receptor subtype selectivity: Allosteric modulators can display selectivity in their ability to enhance the binding of a non-selective orthosteric ligand of one particular subtype relative to other related orthosteric subtypes.

D. Biased modulation: An allosteric ligand can promote more than one type of active state. This results in an agonist-modulator pair having different effects depending on the signaling pathway linked to each receptor. In this example, the modulator increases the potency of an agonist in pathway 1, but decreases the potency of the agonist in pathway 2.

Therapeutic Applications of Allosteric Modulators

The recent expansion in structural knowledge of GPCR allosteric sites is being incorporated into drug design studies. In addition to a number of GPCR allosteric modulators that are in clinical trials, there is increasing excitement about the potential for combining allosteric drugs with existing agents, but non-selective, orthosteric drugs to improve efficacy or to reaprove them.

Appendix: Pharmacological Characterization of GPCR Modulators

- Selectivity of agonist, inverse agonist, and partial agonist.
- Pharmacological characterization of GPCR modulators.

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G protein-coupled receptors (GPCRs) are intrinsically allosteric proteins. They have evolved to transduce signals from one part of the protein to another through spatially distinct, but conformationally linked, binding sites. Endogenous activators bind to the separate orthosteric site of a GPCR, causing a conformational change in the GPCR that allows it to interact with intracellular transducers such as heterotrimic G proteins. This is termed the ‘allosteric transition’. This poster highlights some of the key insights into allosteric mechanisms of GPCR biology.