GPCR Efficacy and Biased Agonism

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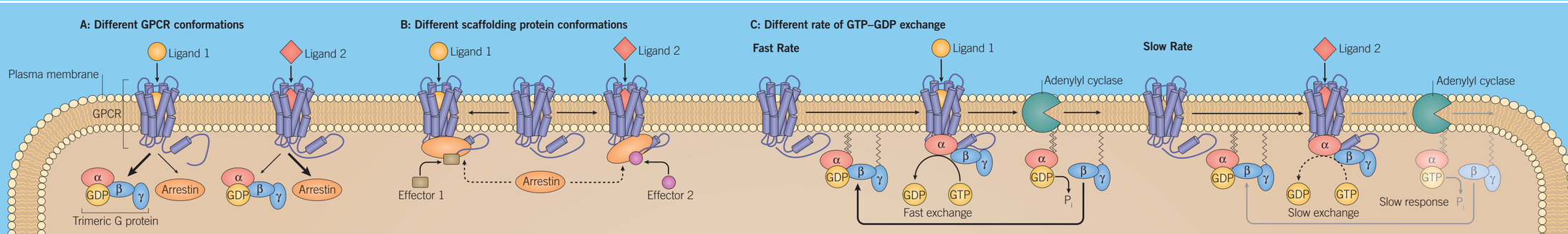
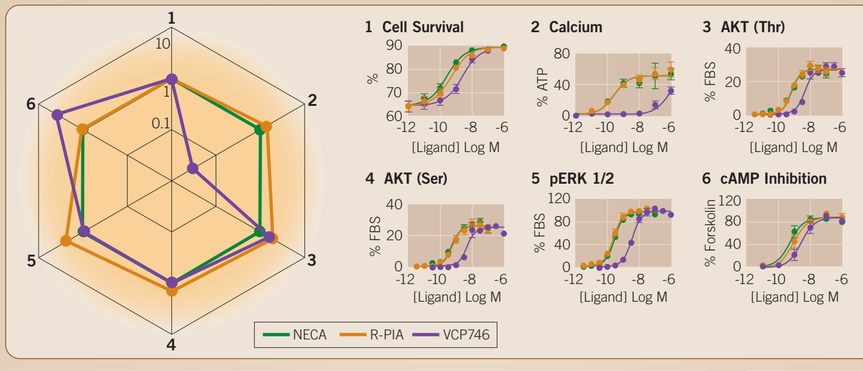


Multiple Mechanisms Elicit Biased Agonism

(**A**) Different ligands induce different conformations within G protein-coupled receptors (GPCRs), promoting binding conditions for particular transducer proteins such as G proteins and arrestins. (**B**) Specific ligand-induced receptor conformations induce different conformational changes within scaffolding proteins such as arrestins, causing activation of distinct downstream signaling pathways. (**C**) Different ligands can control the rate of GTP–GDP exchange through induction of distinct conformational rearrangements within G proteins. Ligands that promote fast GTP association and G protein turnover allow more signaling events to occur than ligands that induce a slow rate of exchange.

G Protein-Coupled Receptors (GPCRs)

GPCRs are seven transmembrane domain receptors, which can move between inactive-like (R, R′ and R″) and active-like (R* and R**) states. This may occur in the absence of ligand or transducer (the Apo state), however the energy barrier to achieving and maintaining active-like conformations means that it's unlikely to occur or has a lower probability in the absence of an agonist and G protein (or other transducer). The presence of both an agonist and transducer (e.g. G protein) stabilizes the active GPCR conformation and gives the highest probability that a signaling event will occur. The rates of transducer engagement and turnover are altered in an agonist dependent manner that determines observed efficacy[1]. Moreover, GPCRs can interact with multiple distinct transducers or regulatory proteins and these can be preferentially engaged in a agonist-specific manner giving rise to biased agonism[1]. Nanobodies that bind to the intracellular face of GPCRs can allosterically drive either inactive or active-like conformations and have been used in structural studies to capture these states[2], however increasing numbers of structures with G proteins are now being solved[3].

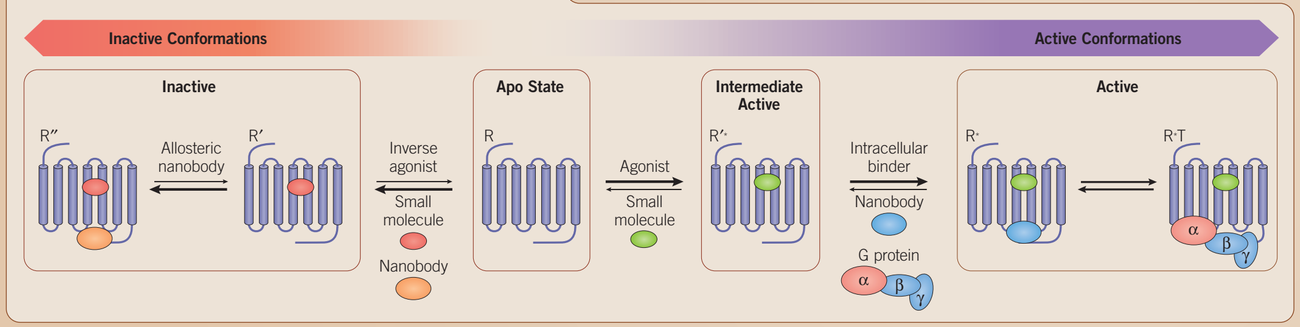


Identifying Biased Agonism at the Adenosine A_1 GPCR (A_1R) Using the Operational Model

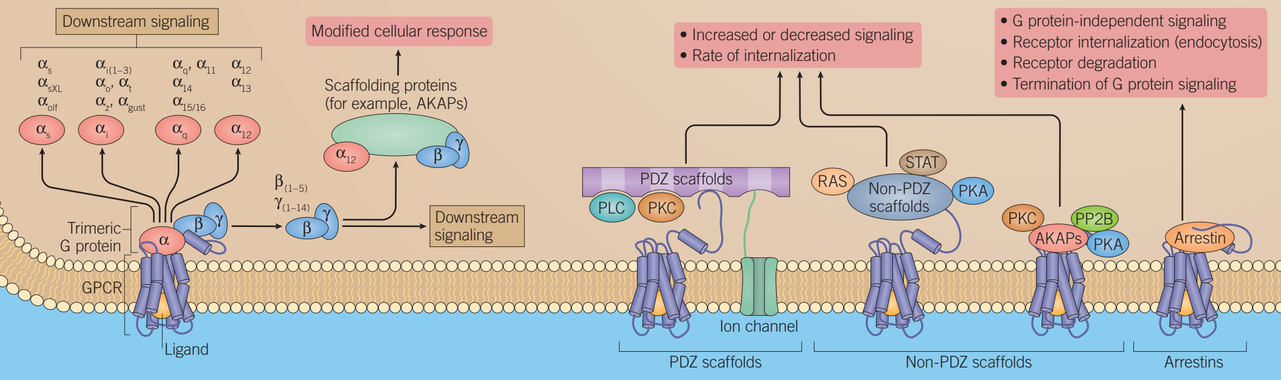
The six concentration-response curves (pictured) show activation of different signaling events for three A_1R agonists, NECA (green line), R-PIA (orange line) and VCP746 (purple line)[4]. Operational modeling was used to derive the transduction ratio ($\log\tau/K_A$; linking agonist occupied receptors to pharmacological effects) and this was plotted in a "Web of Bias"[5].

The "Web of Bias" chart shows each drug profile relative to the reference agonist NECA and reference pathway 1 (as $\Delta\Delta\log\tau/K_A$). Using this visual representation, the biased agonism of VCP746 for pathway 2 (reduced response relative to NECA and pathway 1), is easily observed. In contrast, R-PIA displays a similar signaling profile to the reference agonist, NECA.

Of note, biased agonism is always relative, and must be expressed by comparison with a reference ligand; observations of bias can differ in a system (cell background)-dependent, and temporal manner[1].

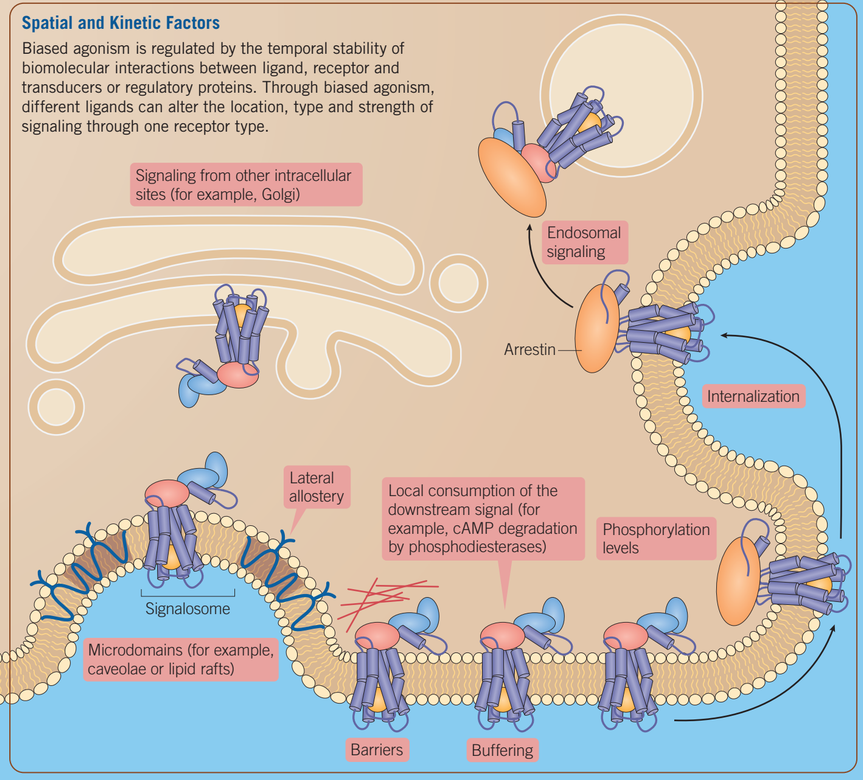


GPCRs are pleiotropically coupled and so can partner with multiple different G proteins (**A**) or other protein transducers (**B**) to regulate intracellular signaling.



Spatial and Kinetic Factors

Biased agonism is regulated by the temporal stability of biomolecular interactions between ligand, receptor and transducers or regulatory proteins. Through biased agonism, different ligands can alter the location, type and strength of signaling through one receptor type.



Therapeutic Application of Biased Agonism

Studying the pharmacology of GPCR biased agonists can help improve the efficacy and safety profiles of drugs. Identification of compounds with a therapeutically beneficial activation profile that have reduced undesired on-target signaling can improve patient outcomes and translation of drugs to the clinic. However, the selection of the most appropriate biased agonists will require improved understanding of the patterns of tissue-specific and integrated signaling that mediate different outcomes both physiologically and in a disease specific context. Collectively, such advances in understanding of disease, combined with advances in drug design, GPCR structure determination and pharmacological assessment of compounds should provide increasing numbers of new biased agonist drugs to the clinic.

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Adenosine A_{2B} Receptors
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- PSB 603
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- MRS 1220
- PSB10

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- SR 59230A
- ICI 118,551
- Xamoterol

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- AM 251
- AM 630
- Cannabigerol
- Org 27569
- PSNCBAM-1

Dopamine Receptors
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- L-741,626
- Fenoldopam
- PAOPA

GABA Receptors
- (*R*)-Baclofen
- CGP 55845
- MRK 016
- TP 003
- CGP 7930

Glutamate (Metabotropic) Receptors
- (*S*)-3,5-DHPG
- LY 341495 disodium salt
- VU 0360172
- ADX 10059

Muscarinic Receptors
- Xanomeline
- (*S*)-(+)-Dimethindene
- VU 0238429

Opioid Receptors
- SNC 80
- Naltrindole
- Meptazinol
- BMS 986187

Purinergic Receptors
- ATPγS tetralithium salt
- MRS 2500
- GW 791343

Trace Amine 1 Receptor
- Ractopamine
- EPPTB

Heterotrimeric G-protein GTPase
SCH 202676
NF 023
G-Protein antagonist peptide
CMPD101

DREADDs
DREADD agonist 21
Perlapine
Salvinorin B
Clozapine *N*-oxide dihydrochloride

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