QSPainRelief

Molecular modelling and dynamic simulations of G protein-coupled receptors (GPCRs)

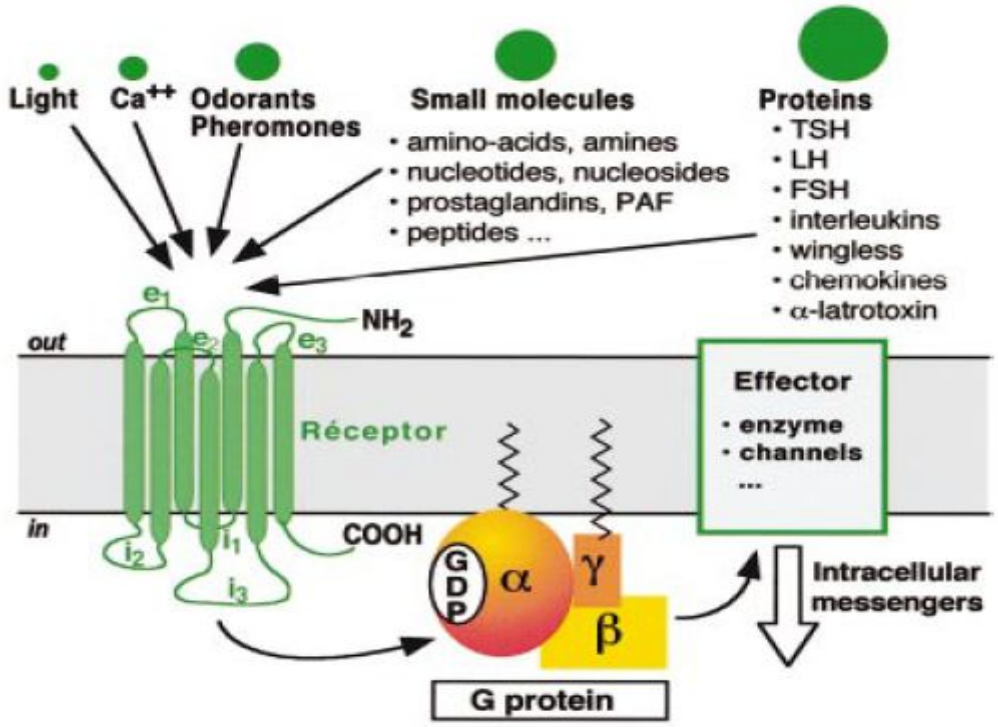
Discover effective novel combination treatments, using existing drugs, in chronic pain treatment

Jesús Giraldo
QSPainRelief Consortium - Universitat Autònoma de Barcelona

3rd GA Meeting 13th – 15th December 2021

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 848068.

G protein-coupled receptors (GPCRs) control signal transmission from outside to inside the cell



Bockaert and Pin EMBO J 1999

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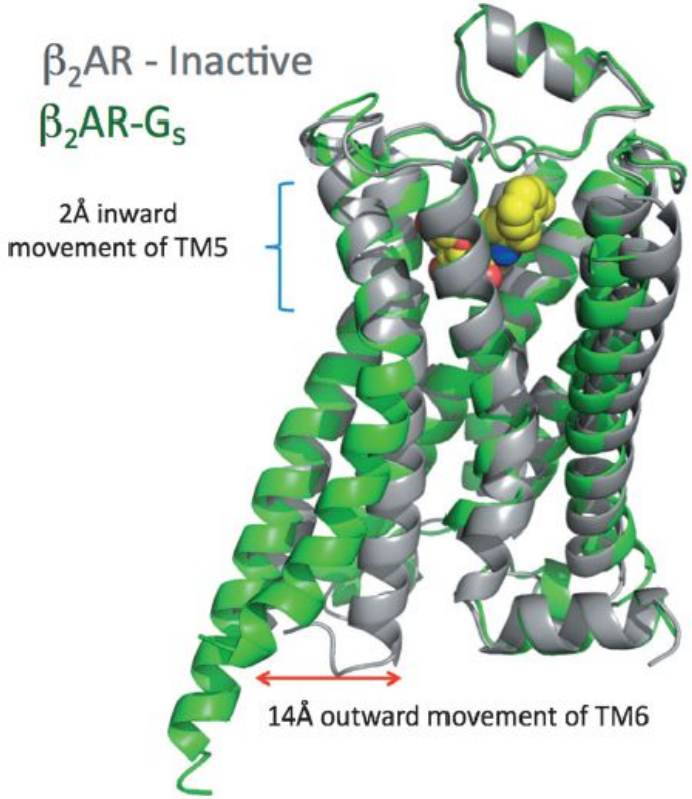
Activation of class A GPCRs implies a conformational change affecting mainly transmembrane helix 6 (TM6)



Kobilka BK Angew Chem Int Ed Engl. 2013

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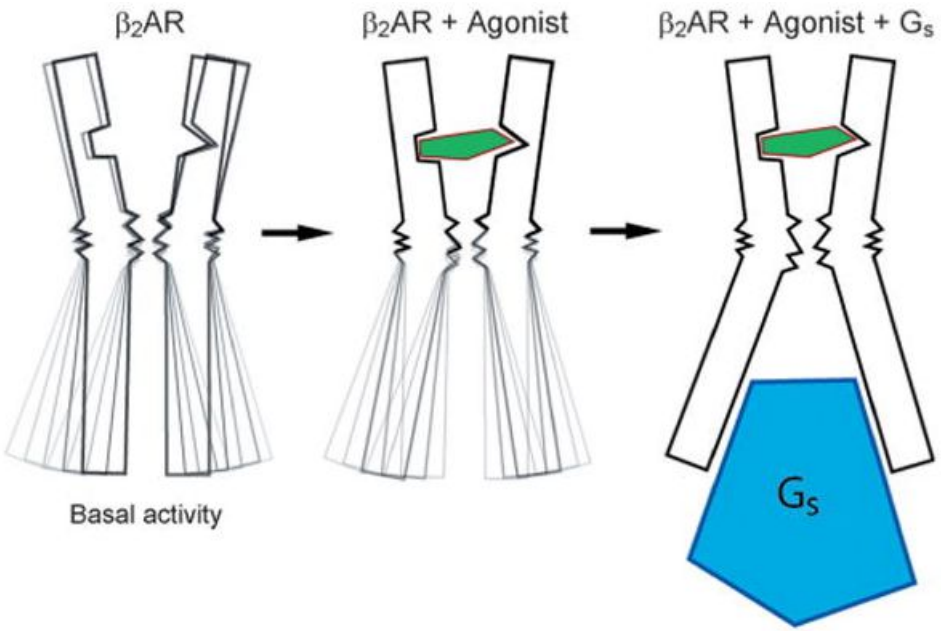
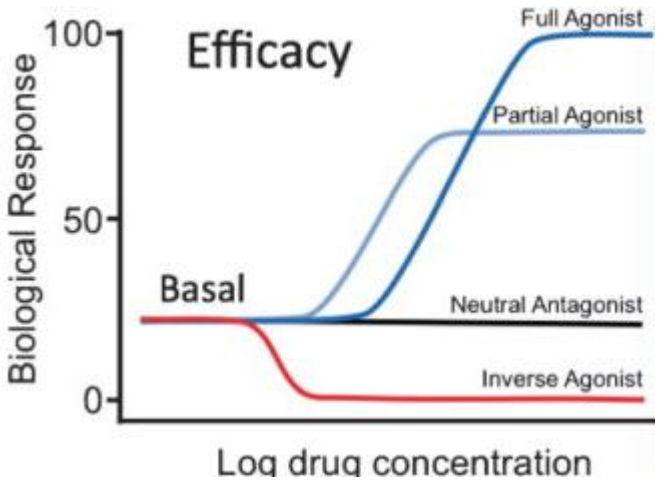
GPCRs are constitutively dynamic entities that are modulated by ligands and transducer proteins





Kobilka BK Angew Chem Int Ed Engl. 2013

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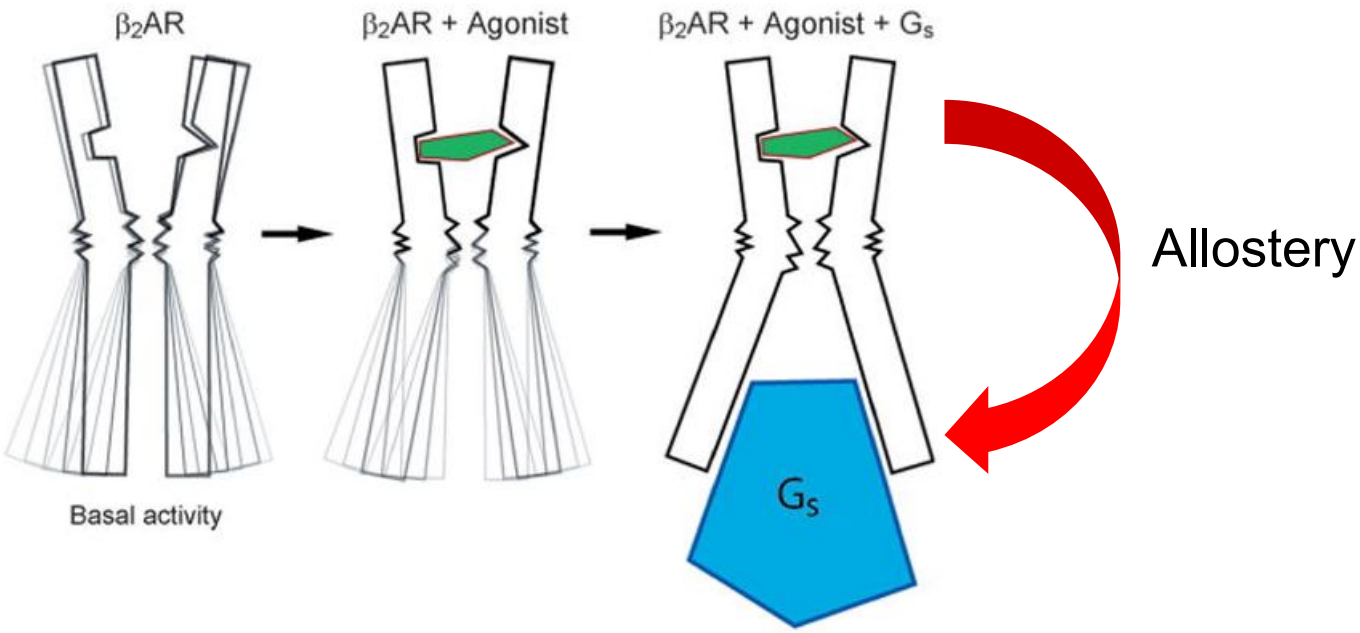
Allostery: a fundamental biological property intrinsic to GPCR function



Adapted from Kobilka BK Angew Chem Int Ed Engl. 2013

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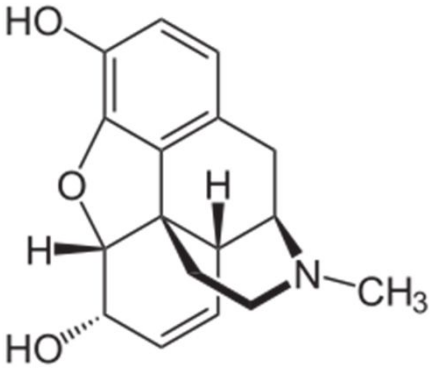
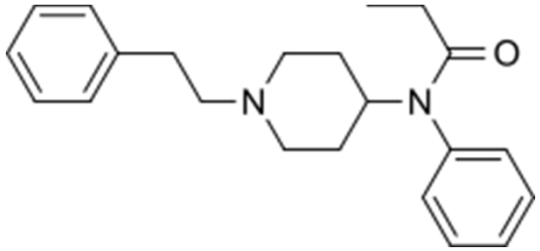
Drugs are chemical entities with particular molecular structure

MOR agonists



MORPHINE



FENTANYL

- Protonable nitrogen atoms
- H-bond donor and acceptor atoms
- Aromatic rings
- Aliphatic rings

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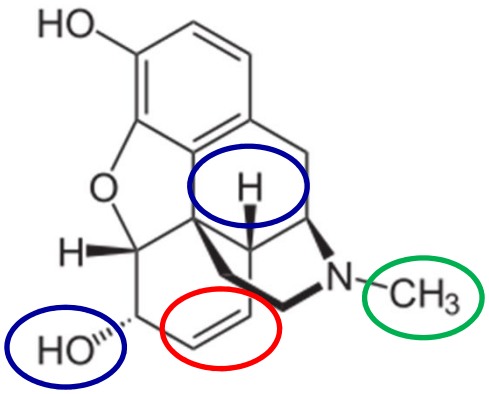
MOR agonists and antagonists: similar but different structures

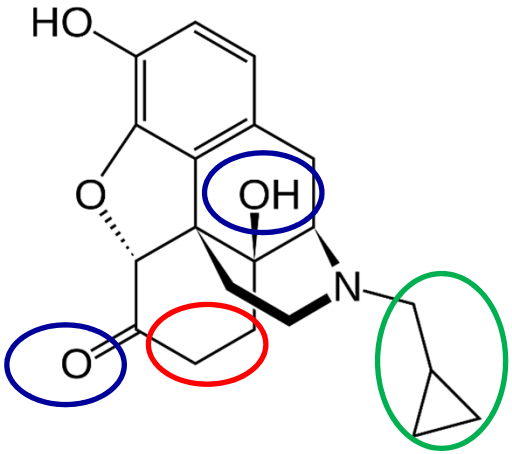
MOR

agonist



MORPHINE

antagonist



NALTREXONE

Globally similar but different in:

- Bond orders
- The position of H-bond donors and acceptors
- The size of the hydrophobic group

Differences in receptor recognition

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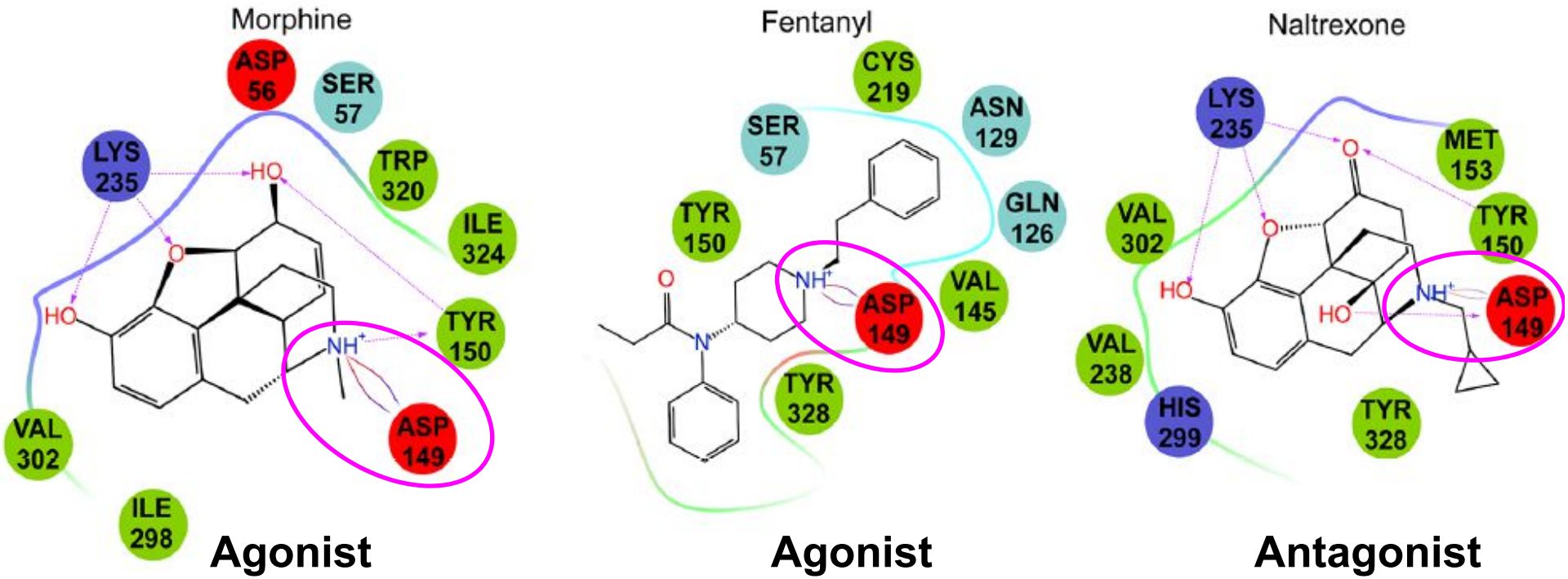
Differences in ligand structures are reflected in receptor recognition: a 2D-representation



Agonist **Agonist** **Antagonist**

Ricarte et al. J Chem Inf Model. 2021

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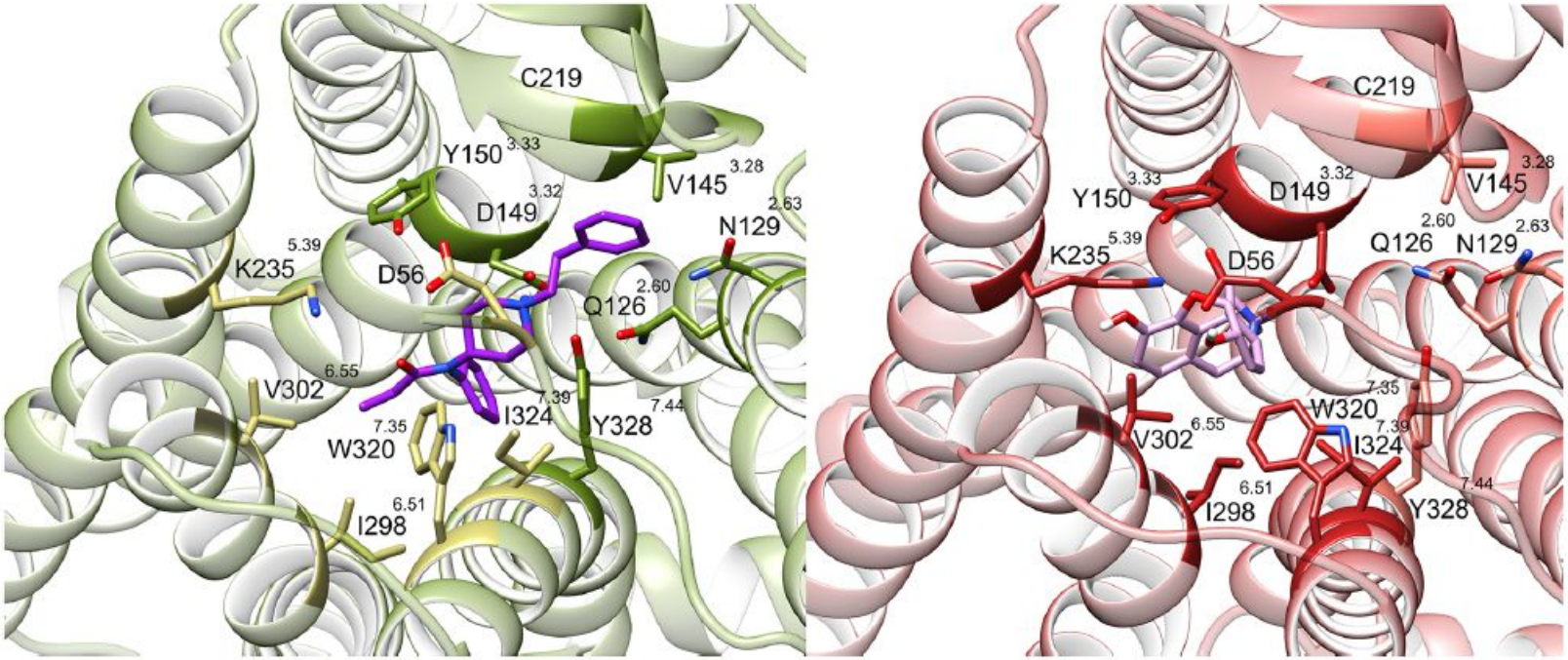
Differences in ligand structures are reflected in receptor recognition: a 3D-representation



Fentanyl Morphine

Ricarte et al. J Chem Inf Model. 2021

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Molecular dynamics simulations are useful in describing ligand-receptor interactions

Full-atom molecular dynamics simulations include atomic representations of

- The receptor
- The bound ligand
- The membrane
- Water molecules
- Lipids and ions

And a force-field to describe the interactions between all the chemical entities in a time-dependent manner.

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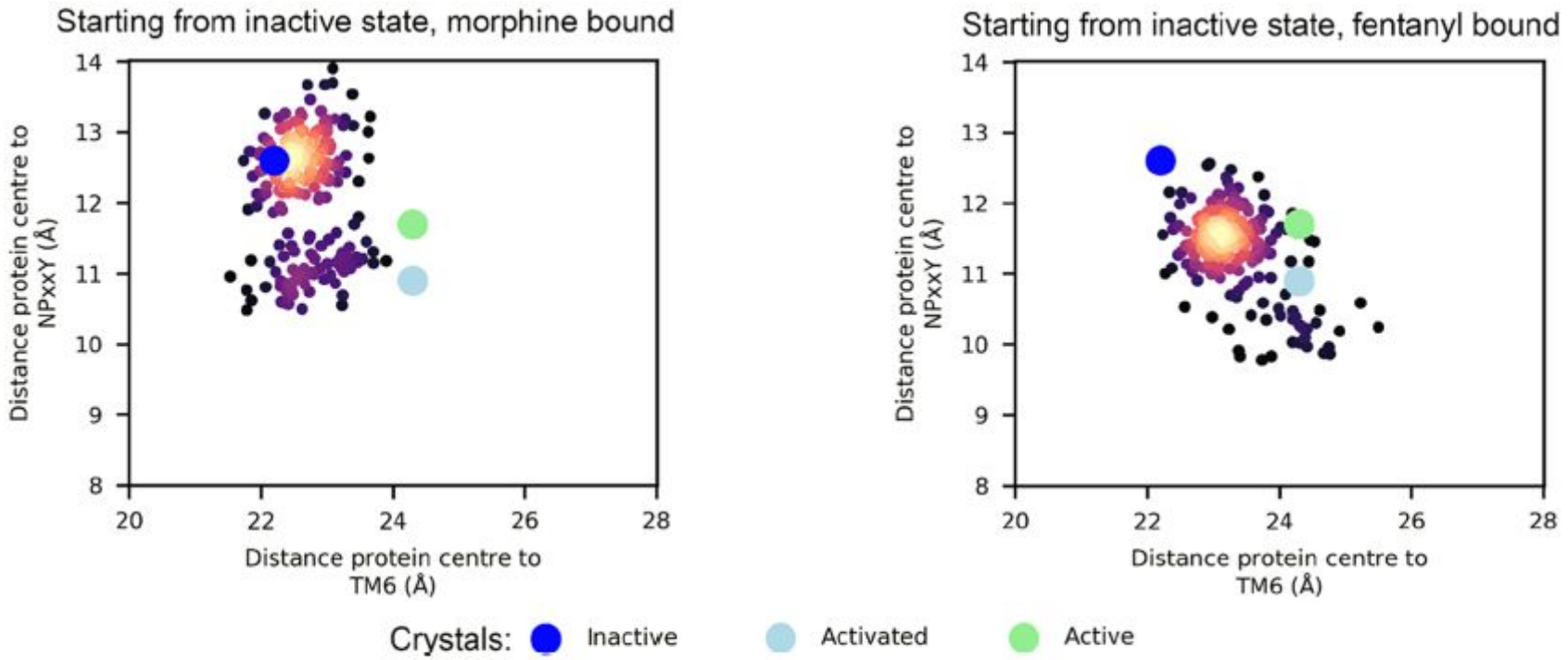
Morphine and fentanyl differ in the pattern of MOR activation



Ricarte et al. J Chem Inf Model. 2021

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The complexity of the problem

The complexity of the problem is manifested in many ways. At the receptor level:

1. The ionic state of the residues of the receptor may be multiple.

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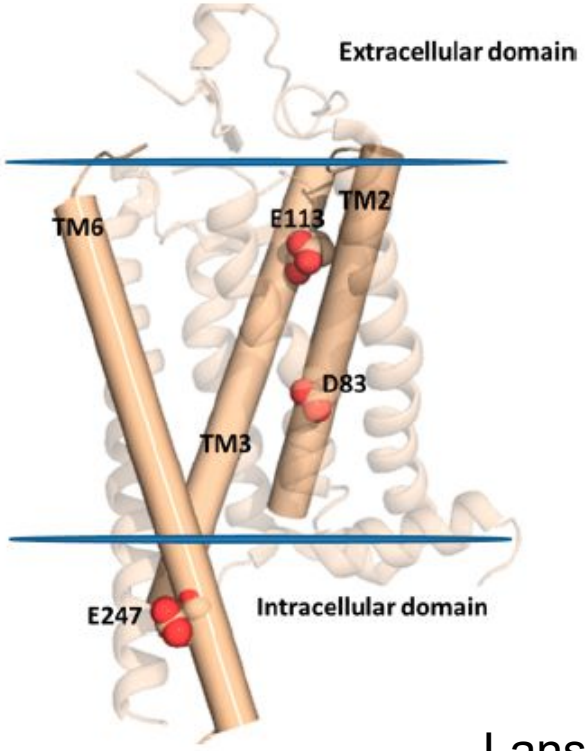
The complexity of the problem at the receptor level: a receptor residue may have multiple ionic states



Selective Protonation of Acidic Residues Triggers Opsin Activation

Protonation of particular acidic residues facilitates opsin activation.

The active species of the receptor may be other than the major receptor species.

Lans et al. J Phys Chem B. 2015

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The complexity of the problem at the receptor level

The complexity of the problem is manifested in many ways. At the receptor level:

1. The ionic state of the residues of the receptor may be multiple.

2. The presence of allosteric sites that can be occupied by small molecules.

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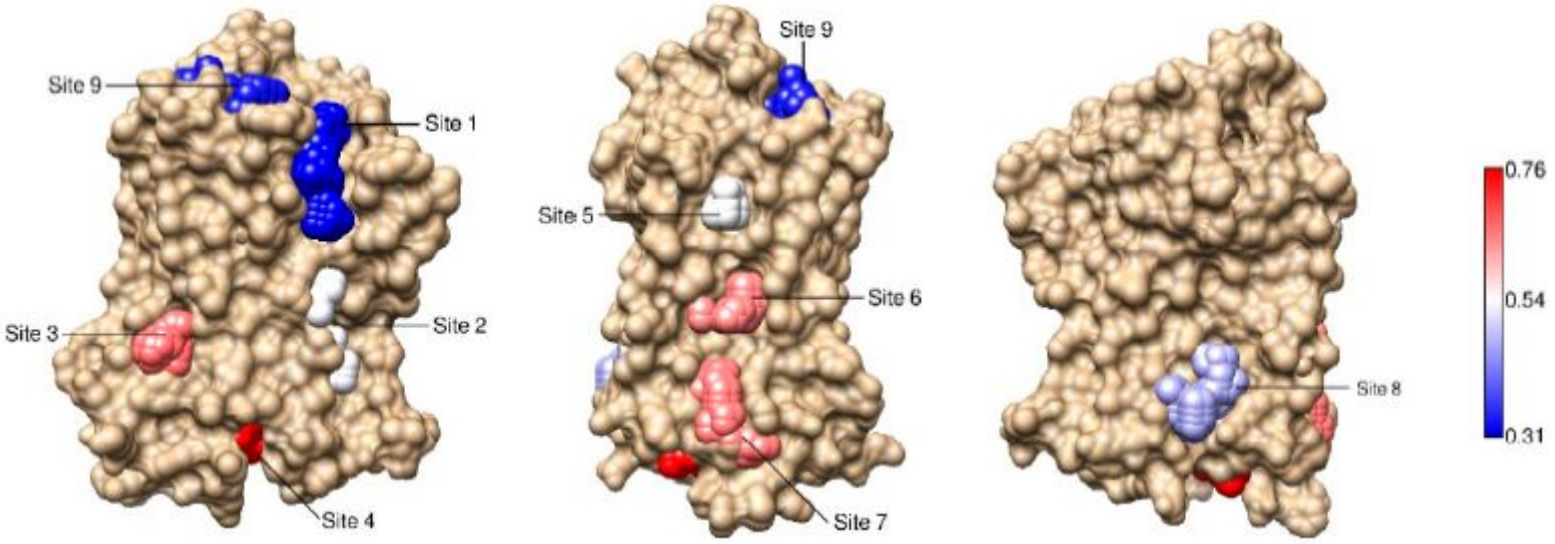
The complexity of the problem at the receptor level: the receptor may have allosteric sites

Computational identification of allosteric sites in the β2-adrenergic receptor



Renault and Giraldo Int J Mol Sci 2020

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The complexity of the problem at the receptor level: the lipidic composition of the membrane

The complexity of the problem is manifested in many ways. At the receptor level:

1. The ionic state of the residues of the receptor may be multiple.

2. The presence of allosteric sites.

3. The lipidic composition of the membrane may affect receptor activation.

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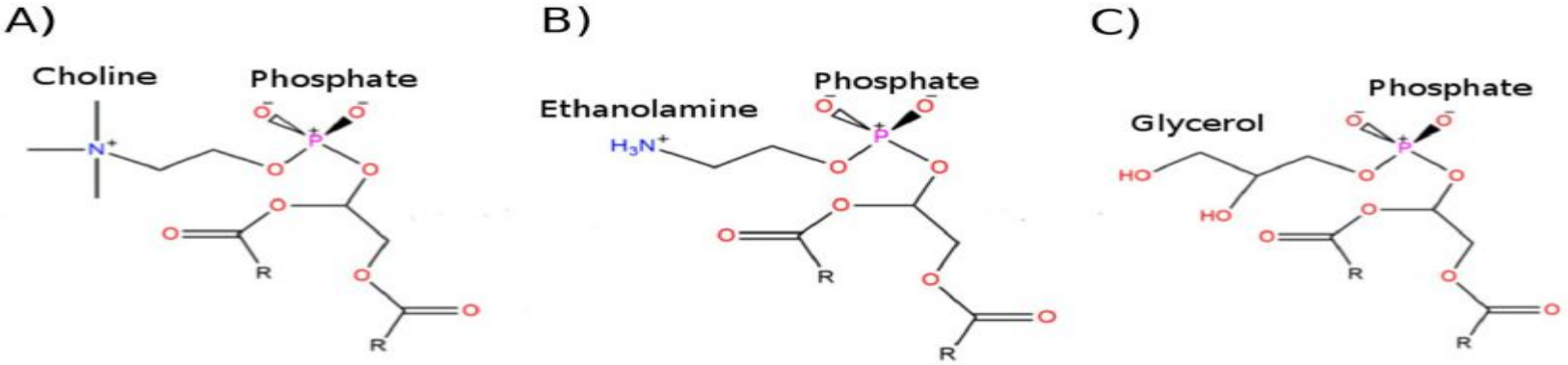
The complexity of the problem at the receptor level: the lipidic composition of the membrane may differ

The lipidic composition of the membrane affects the activation of β2-adrenergic receptor



DOPC
Partial inactivation of the receptor

DOPE
Full inactivation of the receptor

DOPG
Stabilization of an active-like state of the receptor

Bruzzese et al. Sci Rep 2018

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The complexity of the problem through receptor heteromerization

We can consider all these cases as examples of **allosterism within the receptor** but we can consider a different way of allosterism that gives a new layer of complexity to the problem: receptor-receptor interactions.

- Receptors may physically interact forming heteromers.

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The complexity of the problem through receptor heteromerization

Heterodimerization provides a fine-tuning of receptor signaling between different receptors and different neurotransmitters

- **By activating a novel pathway** rather than either protomer autonomous signal cascade.
- **Trans-antagonism**: activation of one receptor inhibits the signaling activity of the other.
- **Trans-activation**: the ability to initiate the signaling cascade of one receptor upon agonist binding to the other protomer.

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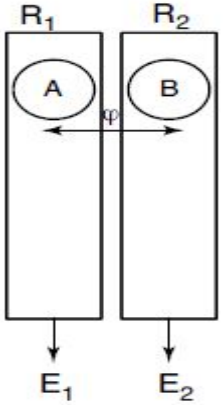
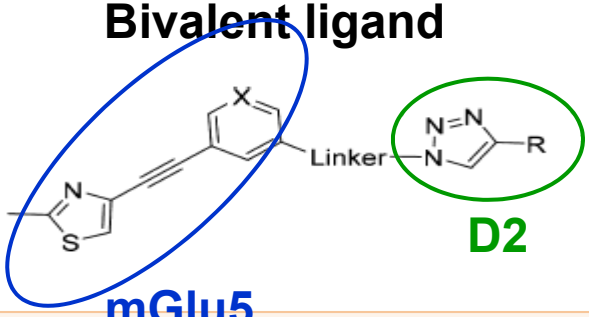
The complexity of the problem through receptor heteromerization

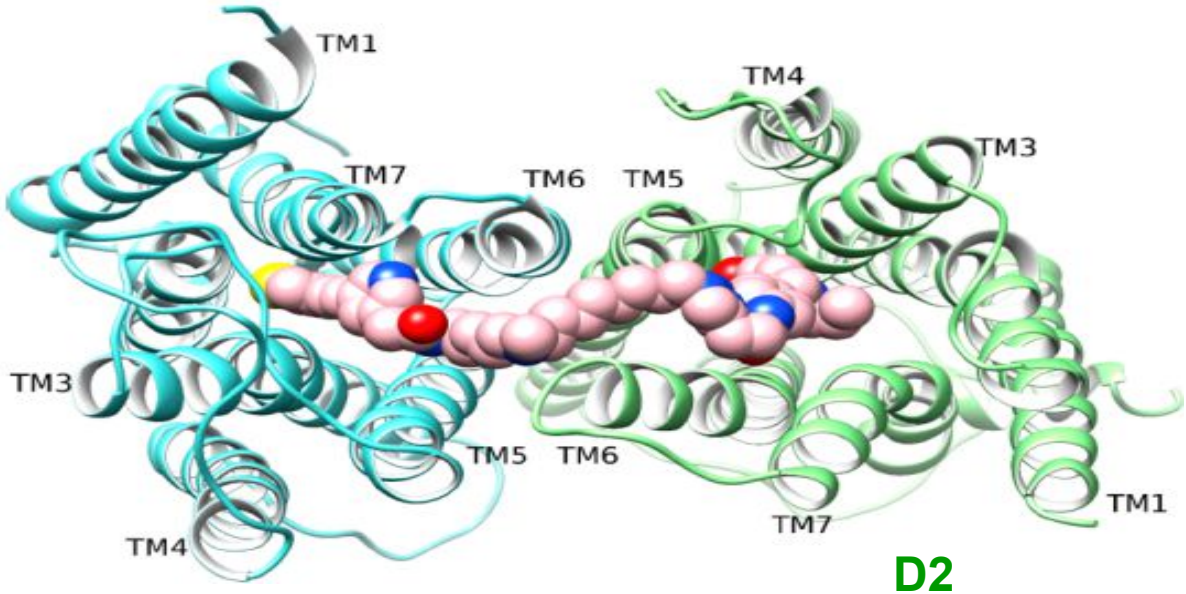
Receptor heterodimer A specific linker length is an indication of heterodimerization



Bivalent ligand



mGlu5 **D2**



mGlu5 **D2**

Qian et al. Journal of Medicinal Chemistry 2018

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Evidences of MOR heteromerization and relation with chronic pain

BJP British Journal of Pharmacology

THEMED ISSUE REVIEW

Therapeutic potential of opioid receptor heteromers in chronic pain and associated comorbidities

Marion Gaborit, Dominique Massotte

First published: 09 December 2021 | https://doi.org/10.1111/bph.15772

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The complexity of the problem through receptor heteromerization

Journal of Medicinal Chemistry

2013

Article

pubs.acs.org/jmc

Bivalent Ligands That Target μ Opioid (MOP) and Cannabinoid1 (CB_1) Receptors Are Potent Analgesics Devoid of Tolerance

Morgan Le Naour,[†] Eyup Akgün,[†] Ajay Yekkirala,[†] Mary M. Lunzer,[†] Mike D. Powers,[†] Alexander E. Kalyuzhny,[‡] and Philip S. Portoghese*[,†]

[†]Department of Medicinal Chemistry, College of Pharmacy, University of Minnesota, Minneapolis, Minneapolis 55455, United States

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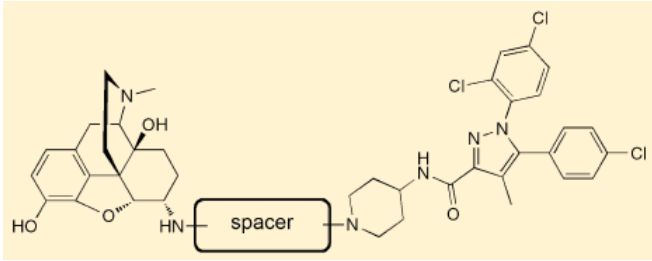

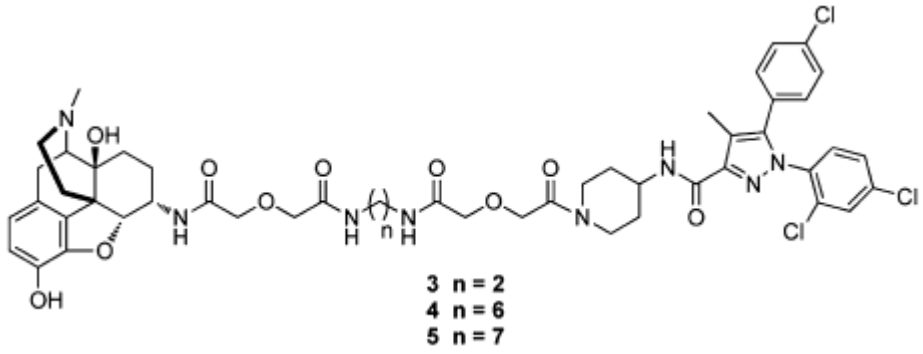

A bivalent ligand composed of a MOR agonist and a CB1 antagonist scaffolds. **Compound 5 with n=7 was the most potent ligand in antinoception experiments**.

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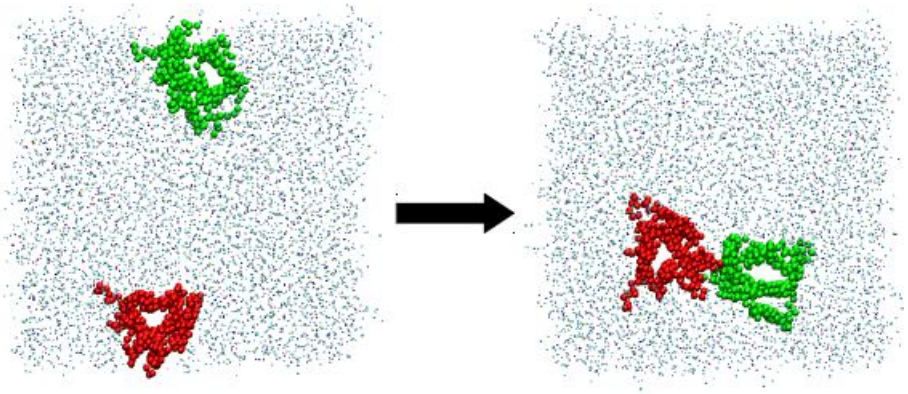
The heteromerization between MOR and CB1 receptors

Coarse-grained molecular dynamics simulations are being performed to assess which are the interfaces for the interaction between MOR and CB1 receptors.

MOR-CB1 self-assembly

- A particular lipidic composition of the membrane.
- A particular force field.
- A high number of simulations to have probability estimates.



Pedro Renault, work in progress

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The heteromerization between MOR and α_{2A}-adrenergic receptors

ARTICLES

2008;4(2):126-31 nature chemical biology

Conformational cross-talk between α_{2A}-adrenergic and μ-opioid receptors controls cell signaling

Jean-Pierre Vilardaga[1,2], Viacheslav O Nikolaev[3,4], Kristina Lorenz[3], Sébastien Ferrandon[1,2], Zhenjie Zhuang[1,2] & Martin J Lohse[3,4]

Morphine binding to the MOR triggers a conformational change in the norepinephrine-occupied alpha2A-AR that inhibits its signaling to G(i) and the downstream MAP kinase cascade. These data highlight a new mechanism in signal transduction whereby a G protein-coupled receptor heterodimer mediates conformational changes that propagate from one receptor to the other and cause the second receptor's rapid inactivation.

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The complexity of the problem through the multiplicity of transducer proteins

The complexity of the problem is manifested in many ways. Third: the multiplicity of transducer proteins (signaling pathways).

1. Allostery within the receptor.
2. Allostery between receptors: receptor heteromerization.
3. GPCRs signal not only through G proteins but also through other transducer proteins.

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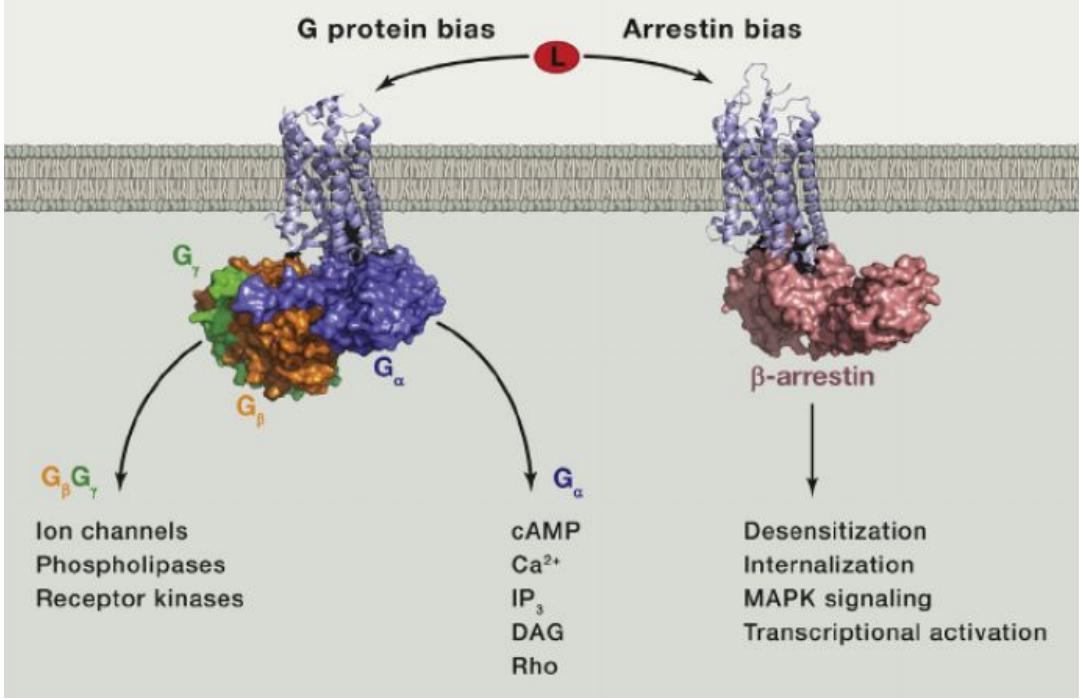
The complexity of the problem through the multiplicity of transducer proteins



GPCRs not only signal through the G protein-dependent pathway but also through G protein-independent pathways such as β-arrestin. Ligands can differentially favor one or the other signaling pathways. This is called **biased signaling or functional selectivity**.

Wacker et al. Cell 2017

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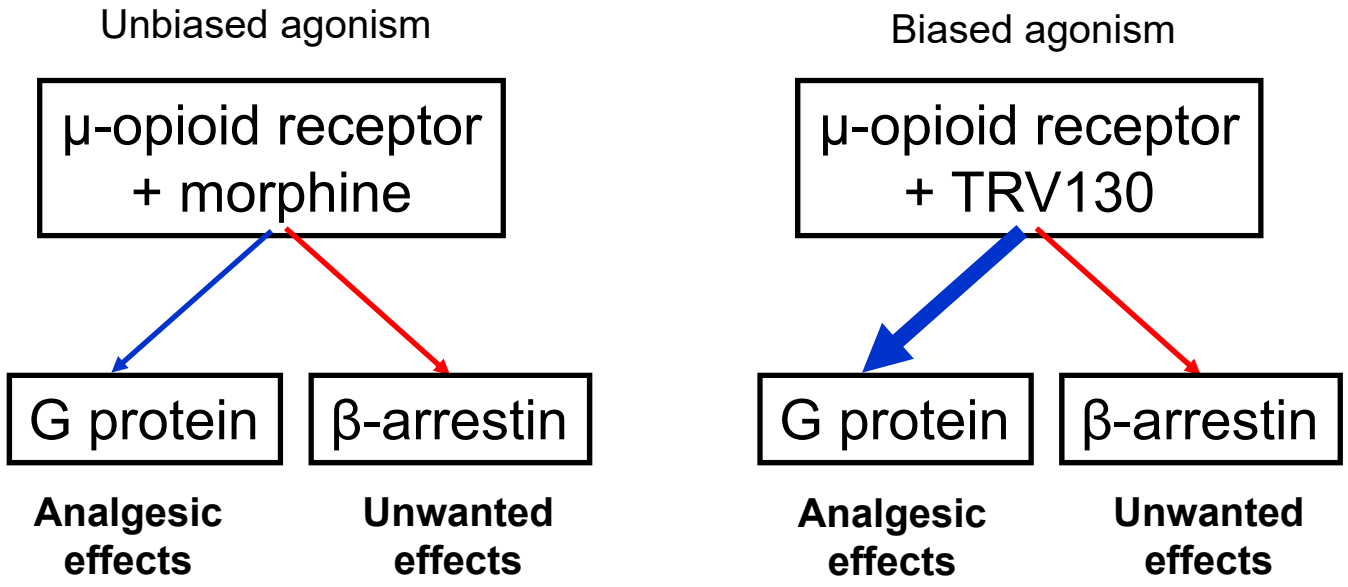
The multiplicity of GPCR pathways may have therapeutic effects



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A change of paradigm in GPCRs

A **change of paradigm** in signal transduction by GPCRs:

- From **vertical** (one receptor; one ligand) to **horizontal** (two interacting receptors: heteromerization; a combination of two ligands).
- From **single** (one signalling pathway) to **multiple** (various signalling pathways: biased agonists).

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From structural models to mechanistic mathematical models.

Mechanistic mathematical models result from applying the chemical laws that govern the proposed reaction path to the law of mass action. There is a correspondence between the equation parameters and the chemical constants of the biological process.

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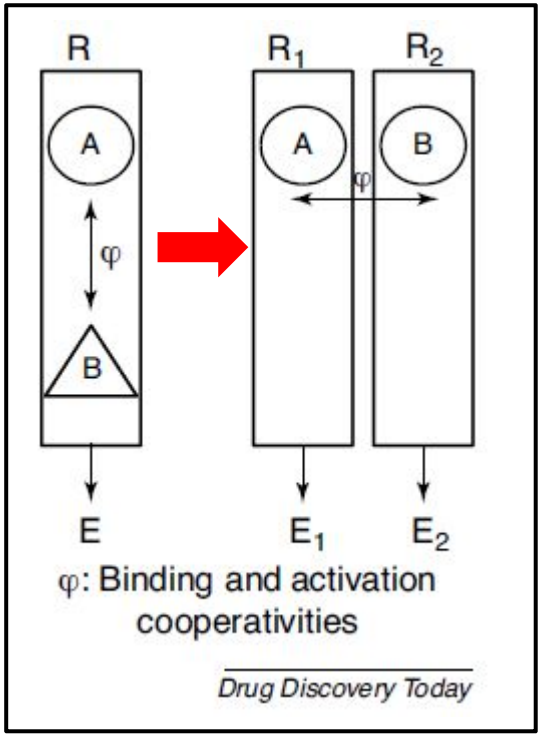
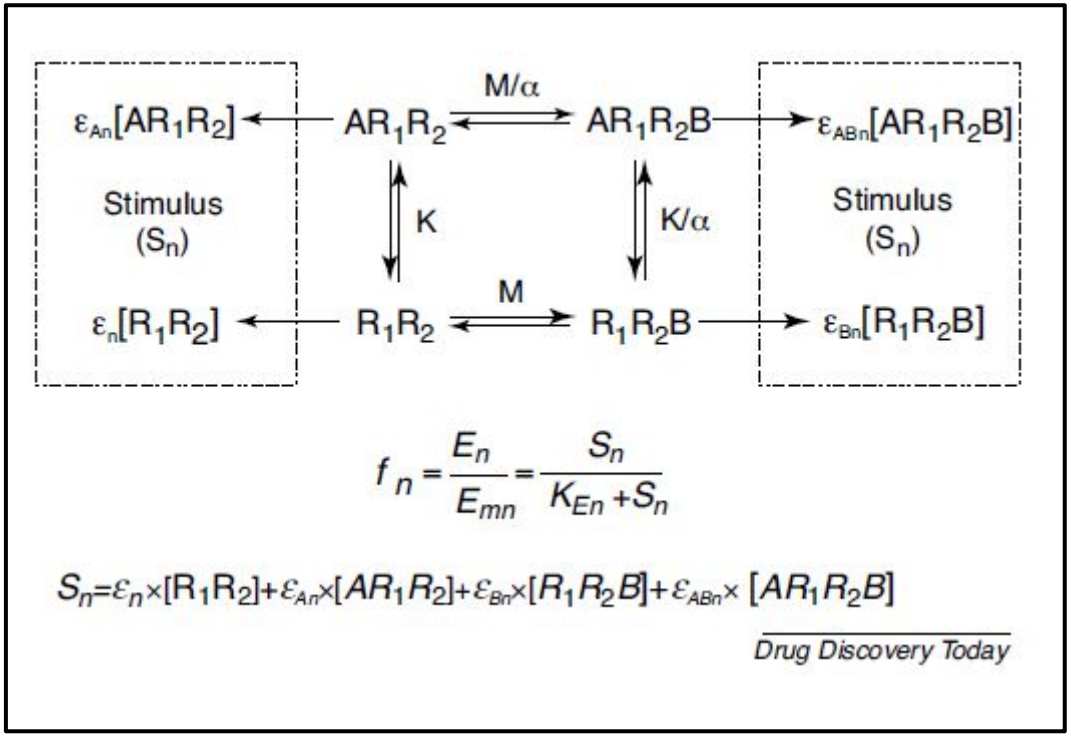
A mathematical model for a GPCR heterodimer





Zhou and Giraldo Drug Discovery Today 2018;23(1):7-11

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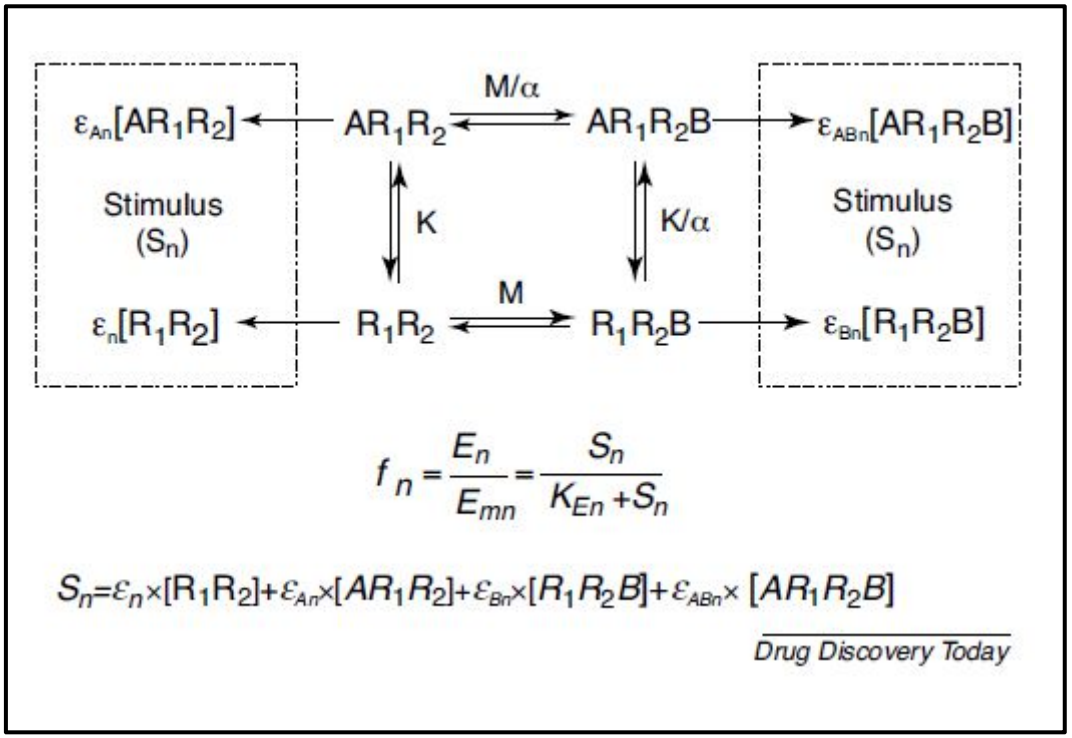
The model can explain typical pharmacological properties: biased agonism, cooperativity between ligands and basal response

- The model can explain **biased agonism** because more than one pathway is considered (n=1,2).
- Cooperativity between A and B is reflected in binding (α) and function ($\varepsilon_{ABn} = \varepsilon_{An} \times \varepsilon_{Bn} \times \delta_n$).
- The model can explain **constitutive receptor activity** (ε_n).
- **Basal response** is defined as

$$f_n = \frac{\varepsilon_n \chi_n}{\varepsilon_n \chi_n + 1}$$

with $\chi_n = [R_1R_2]_T/K_{En}$



Zhou and Giraldo Drug Discovery Today 2018;23(1):7-11

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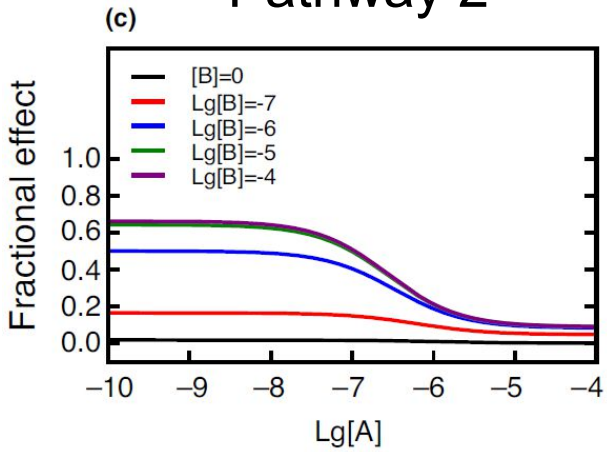
Functional responses can be simulated through the model parameters

Basal response

$$f_n = \frac{\varepsilon_n \chi_n}{\varepsilon_n \chi_n + 1}$$

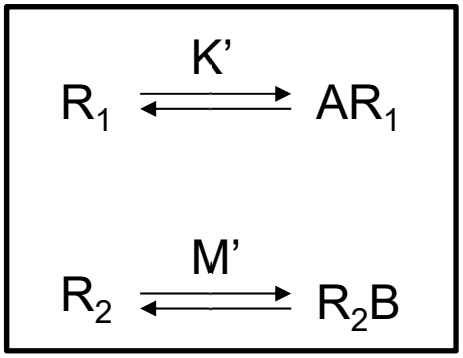
$$\chi_n = [R_1R_2]_T / K_{En}$$

Pathway 2

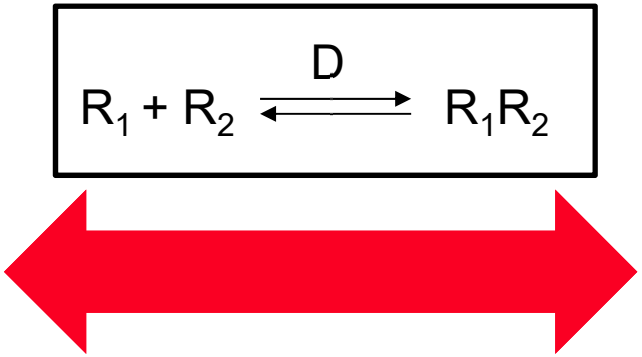


Binding parameters			Functional parameters: pathway 1					Functional parameters: pathway 2				
K	M	α	χ_1	δ_1	ε_1	ε_{A1}	ε_{B1}	χ_2	δ_2	ε_2	ε_{A2}	ε_{B2}
10^{-6}	10^{-6}	10	0.2	5	1	10	0.1	0.2	5	0.1	0.01	10

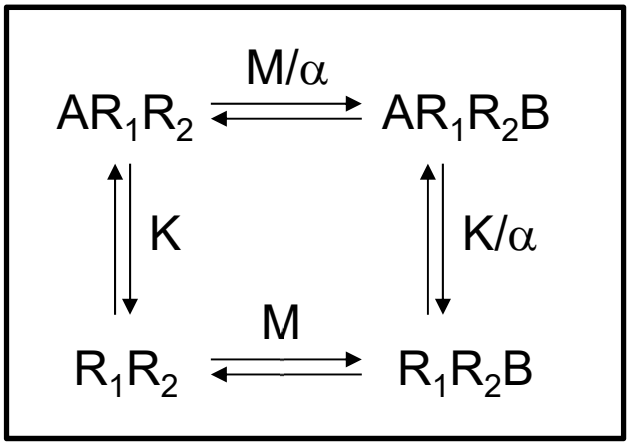
The protomers within the heterodimer can be present in the system as monomers regulated by an equilibrium



Ligand binding to the monomers



The equilibrium constant D connects the monomer and heterodimer scenarios



Ligand binding to the heterodimer

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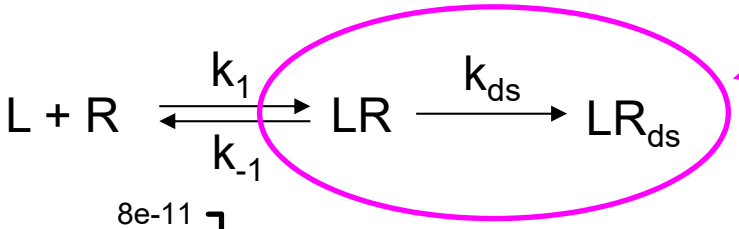
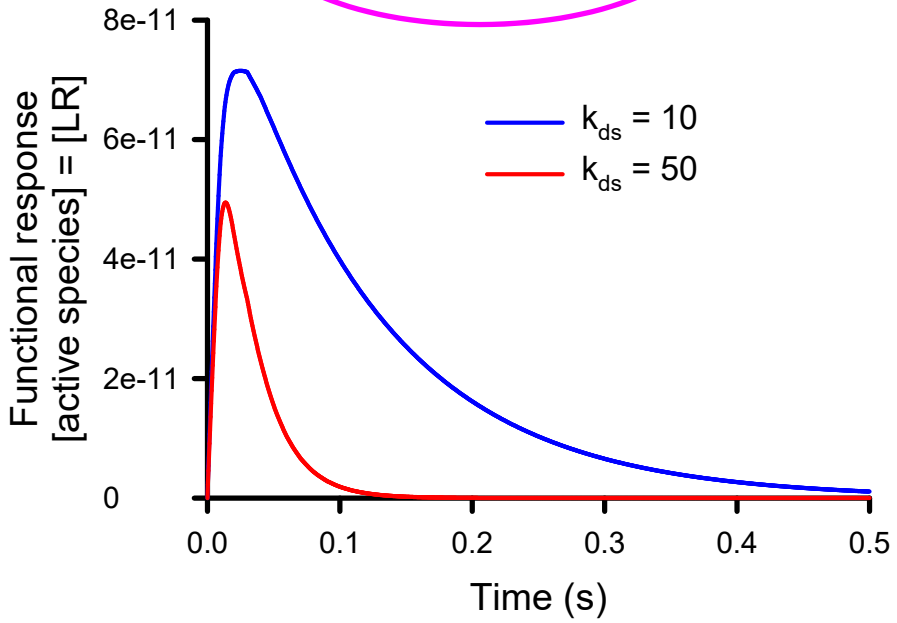
From equilibrium constants to rate constants



Receptor desensitization



Differential equations

$$\frac{d[R]}{dt} = k_{-1}[LR] - k_1[L][R]$$

$$\frac{d[LR]}{dt} = k_1[L][R] - k_{-1}[LR] - k_{ds}[LR]$$

Work in progress: Valdés, Guillamón, Giraldo

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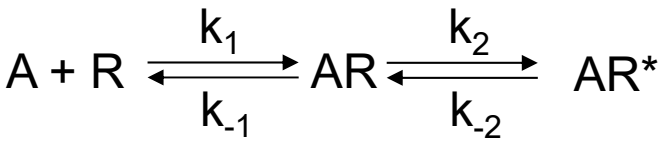
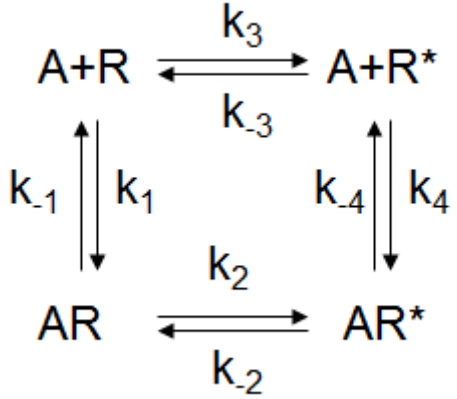
Increasing the complexity of the system (I)

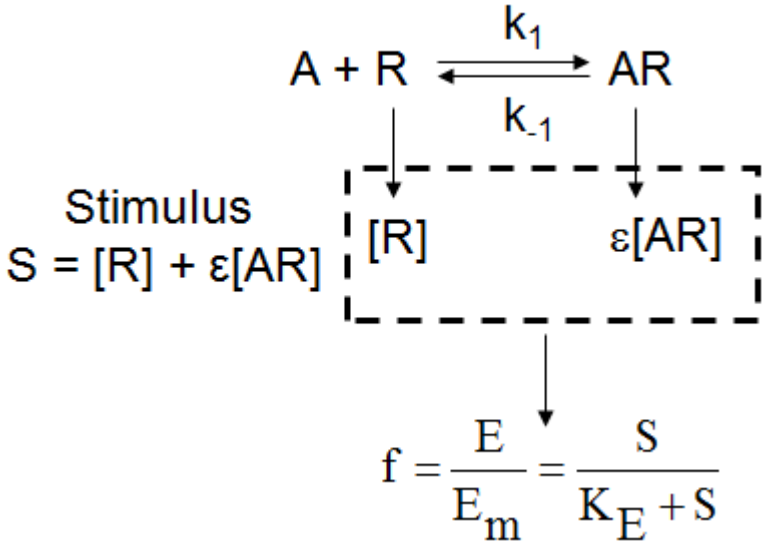
Ligand-induced receptor activation



Constitutive receptor activity:
Two-state model



Constitutive receptor activity:
Operational model



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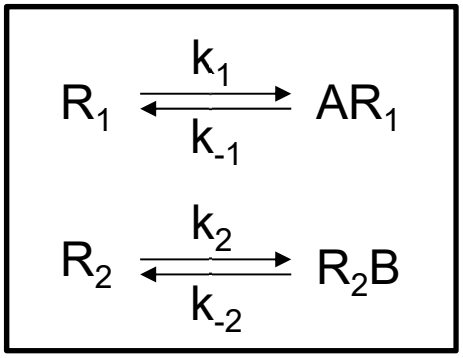
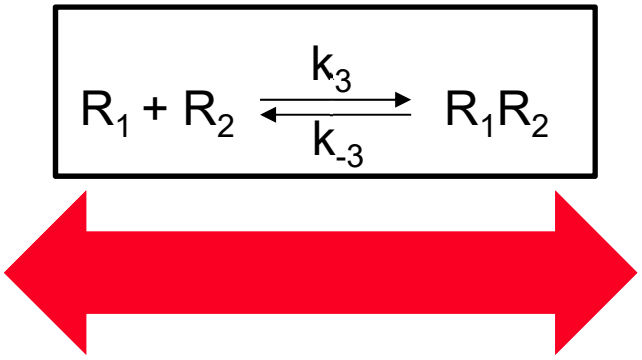
Increasing the complexity of the system (II)

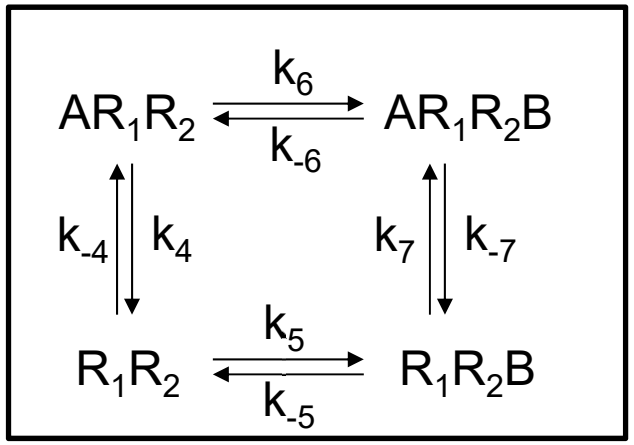
The receptor heterodimer system



Ligand binding to the monomers



Kinetics for the heterodimer formation and dissociation



Ligand binding to the heterodimer

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Conclusions

Pharmacological topics

- ❑ Efficacy, Potency
- ❑ Inverse agonism
- ❑ Cooperativity
- ❑ Allosterism
- ❑ Biased agonism

In the context of

Receptor heteromerization

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