G-protein-coupled receptors

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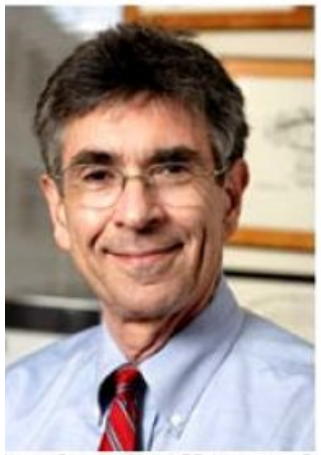
BT-1602

The Nobel Prize in Chemistry 2012 is awarded to Brian K. Kobilka (57) and Robert J. Lefkowitz (69) for studies of GPCRs.



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Robert J. Lefkowitz

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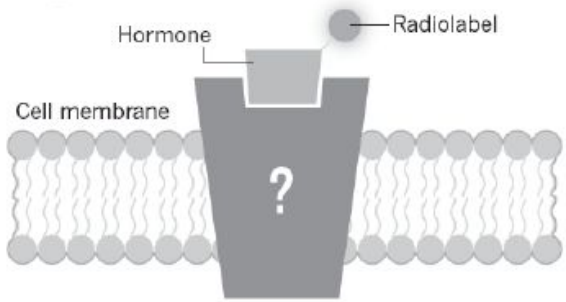
Brian K. Kobilka

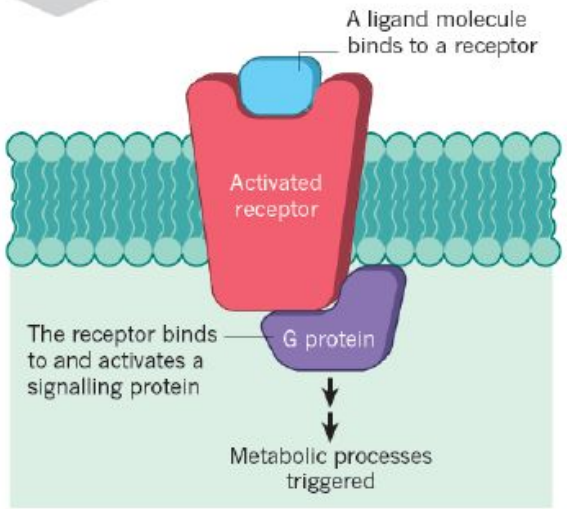
1968

Lefkowitz began using radiolabelled hormones to identify several of the receptors that enable cells to sense their environment.



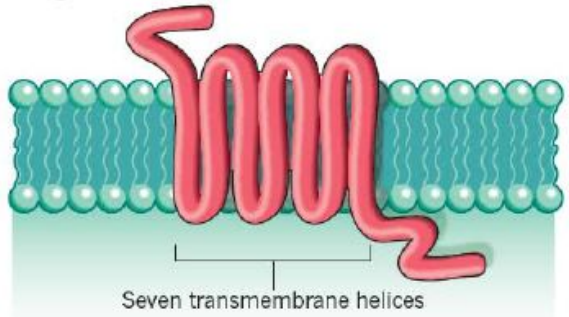
1980

Lefkowitz and colleagues proposed the widely accepted 'ternary complex model' for receptor activation.



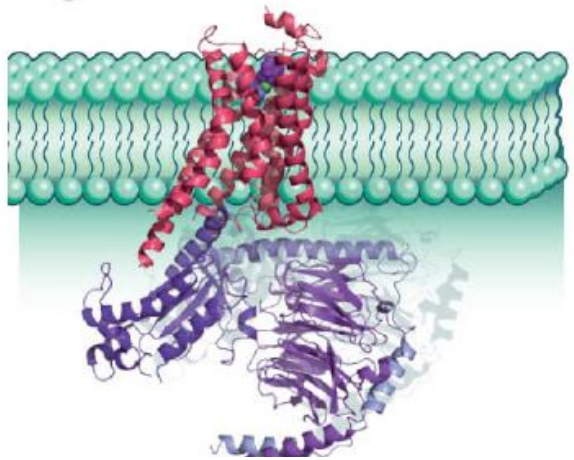
1986

Lefkowitz, Kobilka and co-workers cloned the gene that encodes the β_2-adrenergic receptor, revealing its transmembrane structure. They concluded that it was part of a family of functionally similar receptors.

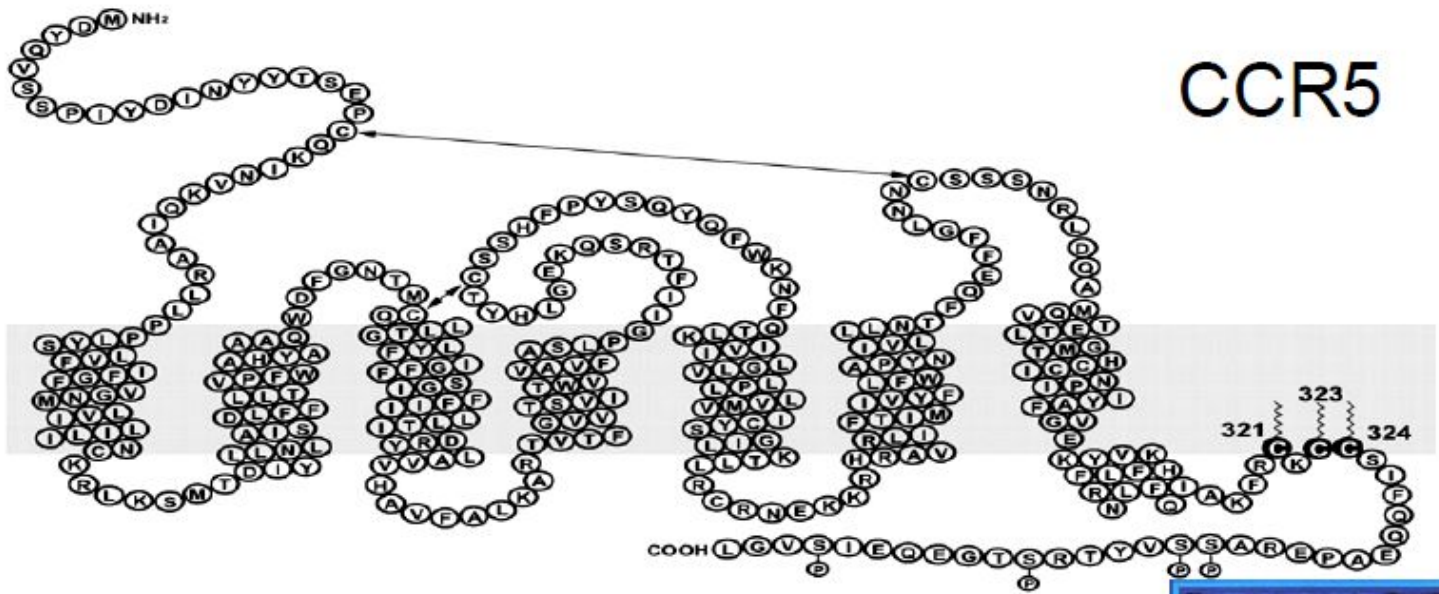


2011

Kobilka and colleagues solved the crystal structure of the β_2-adrenergic receptor in complex with an activating ligand and a G protein.



- G protein-coupled receptors (GPCRs)
- Seven transmembrane receptors (7 TM receptors)
- Heptahelical receptors
- Serpentine receptors



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- protein–coupled receptors are found only in eukaryotes, including yeast, and animals.
- The ligands that bind and activate these receptors include light-sensitive compounds, odors, pheromones, hormones, and neurotransmitters, and vary in size from small molecules to peptides to large proteins.
- G protein–coupled receptors are involved in many diseases, and are also the target of approximately 40% of all modern medicinal drugs.

- There are two principal signal transduction pathways involving the G protein–coupled receptors:
- the cAMP signal pathway and
- the phosphatidylinositol signal pathway

Physiological roles

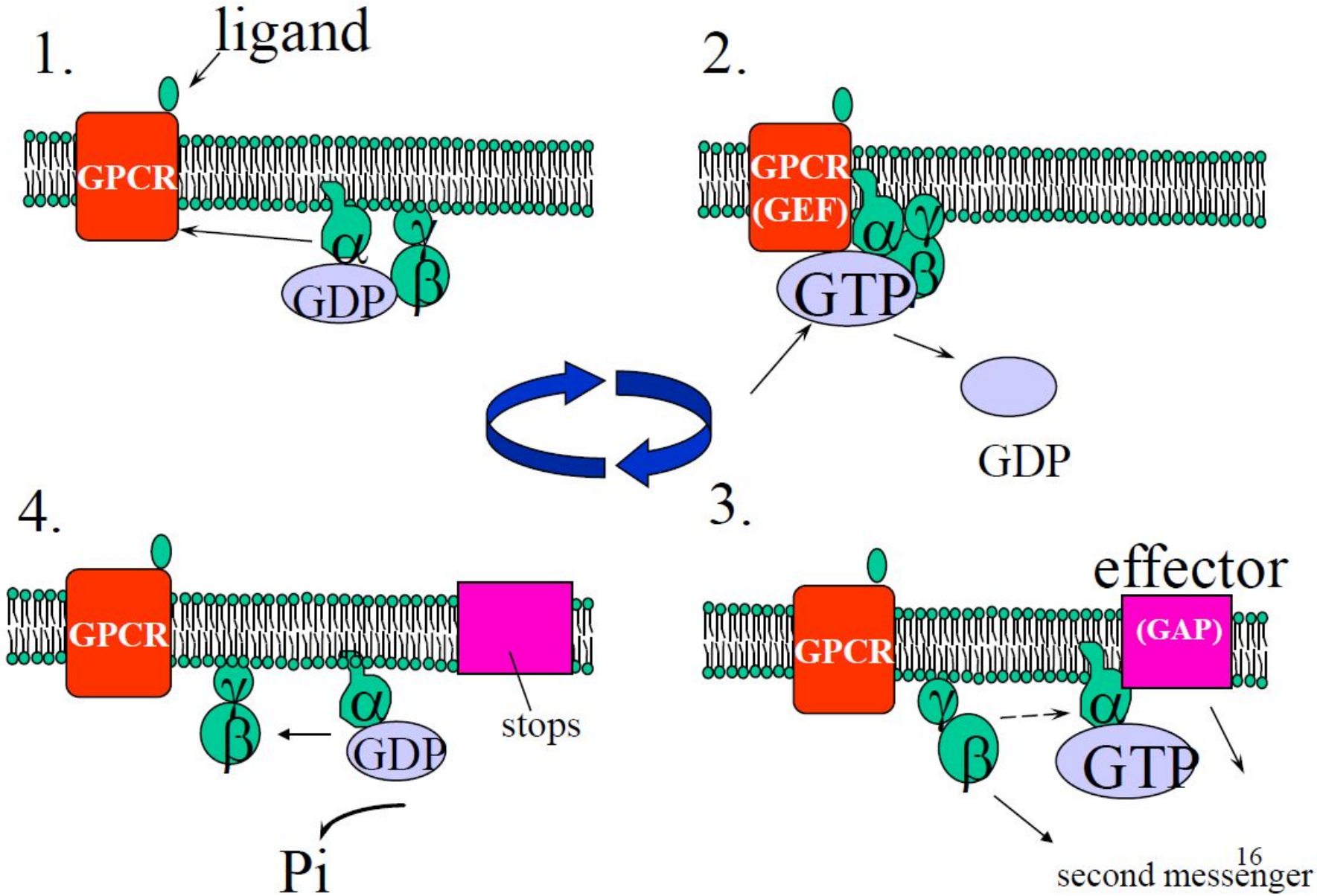
GPCRs are involved in a wide variety of physiological processes. Some examples of their physiological roles include:

- The visual sense: The opsins use a photoisomerization reaction to translate electromagnetic radiation into cellular signals. Rhodopsin, for example, uses the conversion of *11-cis*-retinal to *all-trans*-retinal for this purpose
- The gustatory sense (taste): GPCRs in taste cells mediate release of gustducin in response to bitter- and sweet-tasting substances.
- The sense of smell: Receptors of the olfactory epithelium bind odorants (olfactory receptors) and pheromones (vomeronasal receptors)
- Behavioral and mood regulation: Receptors in the mammalian brain bind several different neurotransmitters, including serotonin, dopamine, GABA, and glutamate
- Regulation of immune system activity and inflammation: Chemokine receptors bind ligands that mediate intercellular communication between cells of the immune system; receptors such as histamine receptors bind inflammatory mediators and engage target cell types in the inflammatory response. GPCRs are also involved in immune-modulation and directly involved in suppression of TLR-induced immune responses from T cells.
- Autonomic nervous system transmission: Both the sympathetic and parasympathetic nervous systems are regulated by GPCR pathways, responsible for control of many automatic functions of the body such as blood pressure, heart rate, and digestive processes
- Cell density sensing: A novel GPCR role in regulating cell density sensing.
- Homeostasis modulation (e.g., water balance).
- Involved in growth and metastasis of some types of tumors.

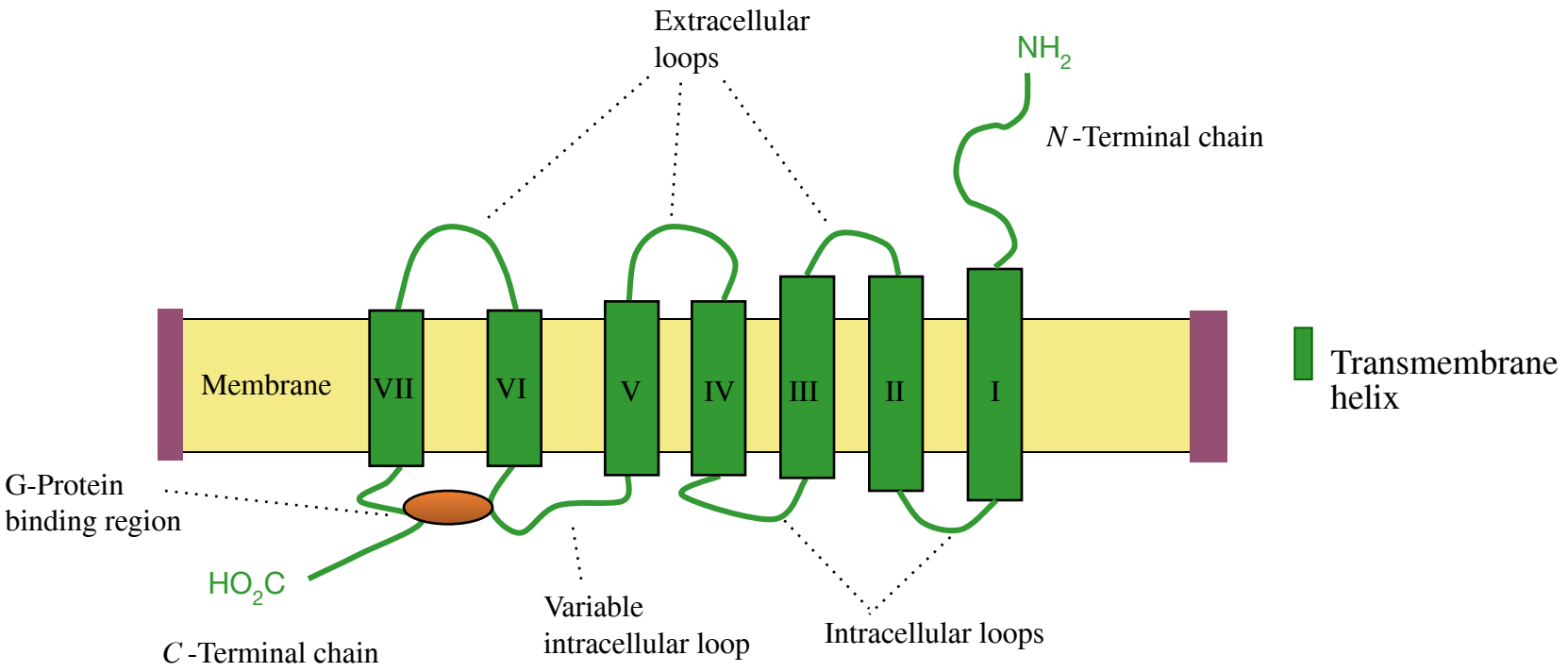
G-protein-coupled receptor (GPCR) families

- Class A Rhodopsin like
- Class B Secretin like
- Class C Metabotropic glutamate / pheromone
- Class D Fungal pheromone
- Class E cAMP receptors (Dictyostelium)
- Frizzled/Smoothened family

G protein action



Structure - Single protein with 7 transmembrane regions



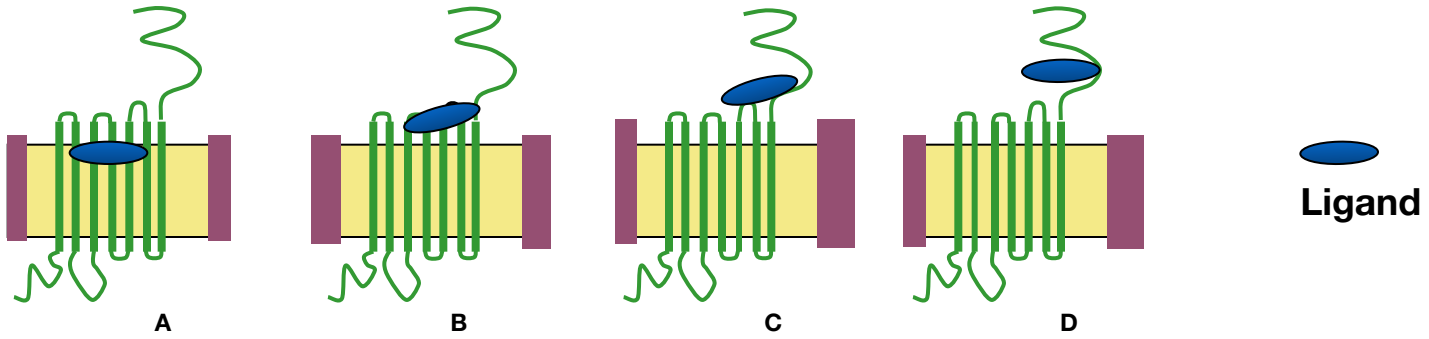
G-protein-coupled receptors (7-TM receptors)

Ligands

- **Monoamines e.g. dopamine, histamine, noradrenaline, acetylcholine (muscarinic)**
- **Nucleotides**
- **Lipids**
- **Hormones**
- **Glutamate**
- **Ca^{++}**

G-protein-coupled receptors (7-TM receptors)

Ligand binding site - varies depending on receptor type



A) Monoamines - pocket in TM helices

B) Peptide hormones - top of TM helices + extracellular loops + *N*-terminal chain

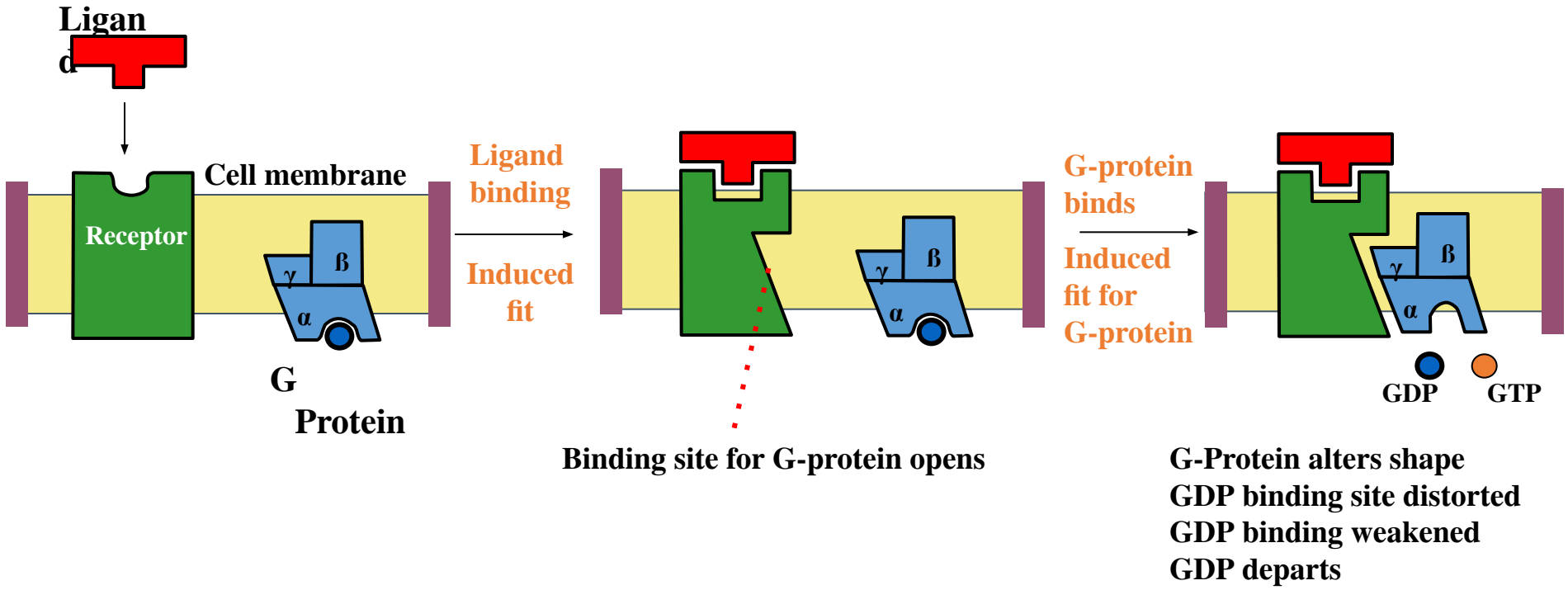
C) Hormones - extracellular loops + *N*-terminal chain

D) Glutamate - *N*-terminal chain

3. G-protein-coupled receptors (7-TM receptors)

3.6 Signal transduction pathway

a) Interaction of receptor with G_s-protein



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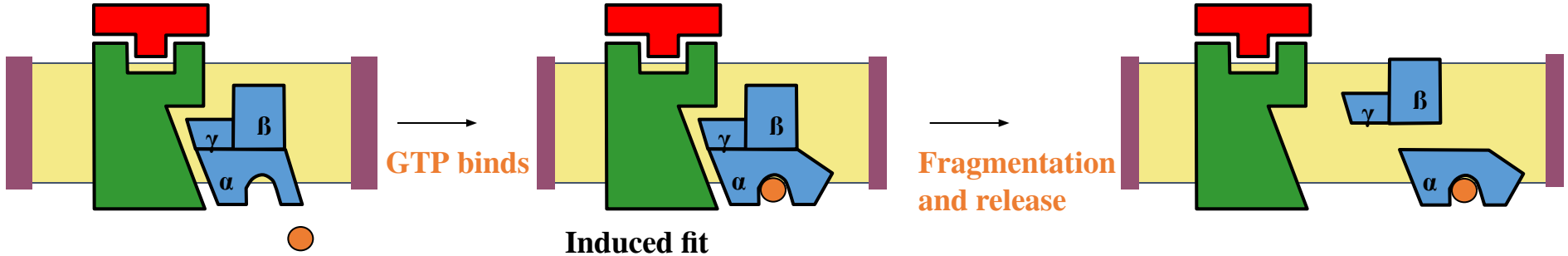


Binding site recognises GTP

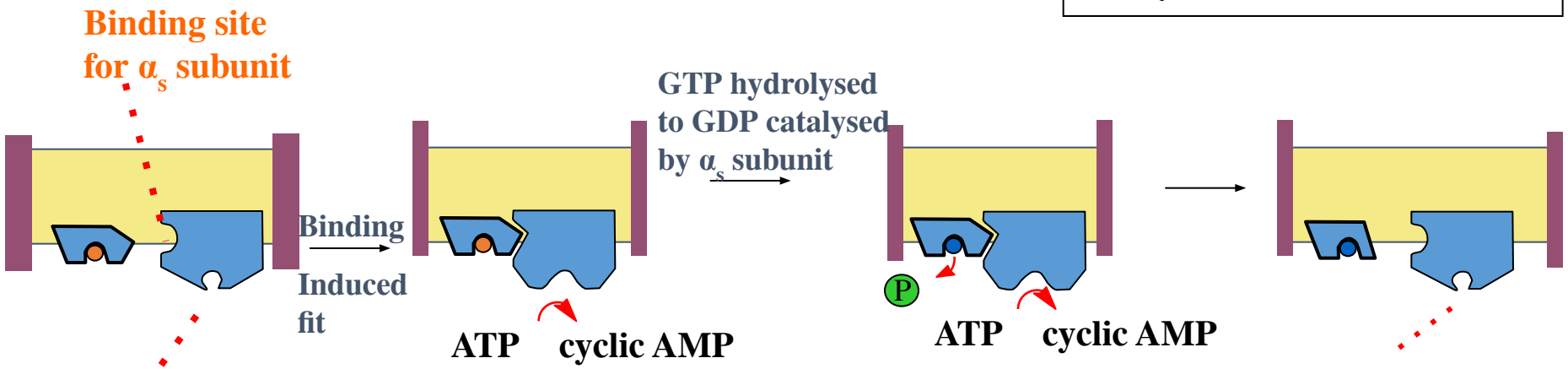
Induced fit
G-protein alters shape
Complex destabilised

- Process repeated for as long as ligand bound to receptor
- Signal amplification - several G-proteins activated by one ligand
- α_s Subunit carries message to next stage

3. G-protein-coupled receptors (7-TM receptors)

3.6 Signal transduction pathway

b) Interaction of α_s with adenylate cyclase

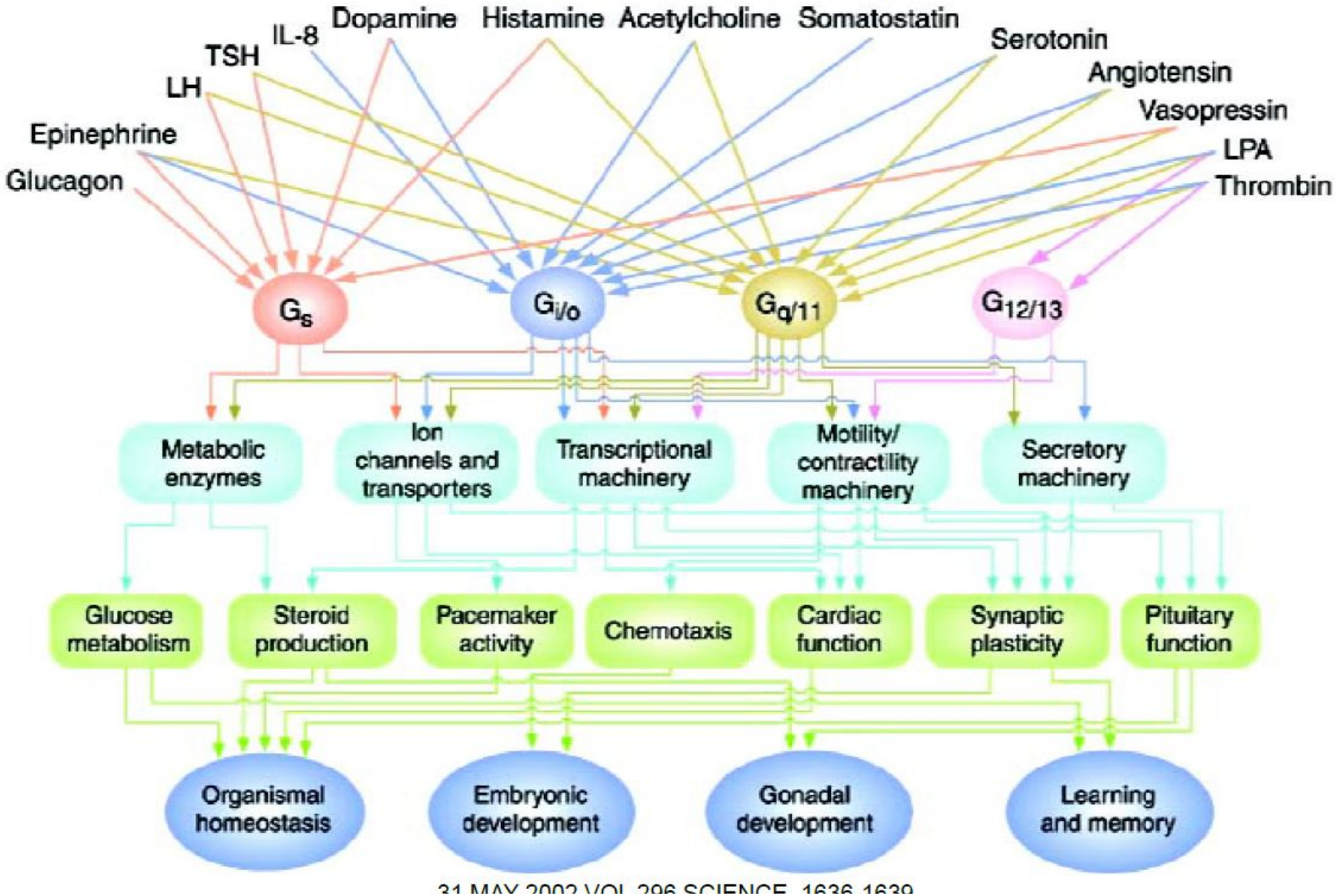


Signal transduction (con)

α_s Subunit changes shape
Weaker binding to enzyme
Departure of subunit
Enzyme reverts to inactive state

→ α_s Subunit recombines with β,γ dimer to reform G_s protein

Regulation of systemic functions by signaling through G protein pathways



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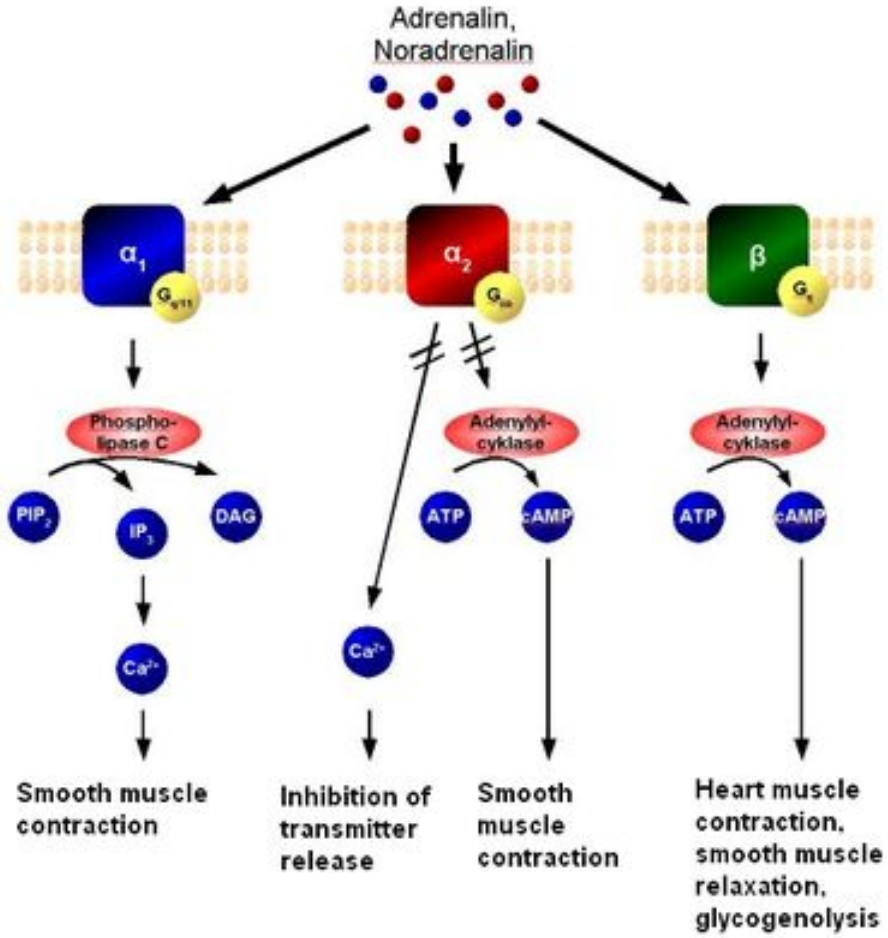
Heterotrimeric G-protein α-subunit subfamilies and their effects

G protein	α-subunit subfamily	Effect of activation
G_s	$G_s\alpha$, $G_{olf}\alpha$	Stimulation of adenylyl cyclase
G_i	$G_i\alpha_{1-3}$, $G_o\alpha$, $G_z\alpha$ $G\alpha_t$	Inhibition of adenylyl cyclase Activation of cGMP phosphodiesterase (specific for retinal phototransduction)
G_q	$G_q\alpha$, $G_{11}\alpha$, $G_{14}\alpha$, $G_{16}\alpha$	Activation of phospholipase Cβ (PLCβ)
G_{12}	$G_{12}\alpha$, $G_{13}\alpha$	Activation of RhoA signalling; activation of PLCε

Adrenoreceptor

Localization and the main effects

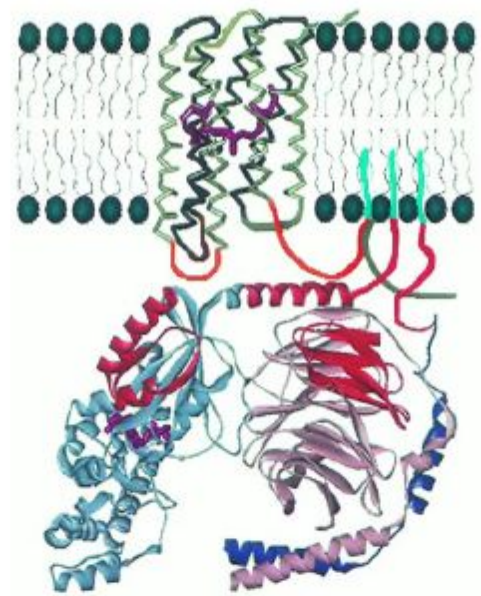
- **α_1- и β_1**- receptors localized mainly in the postsynaptic membrane and react to the action of noradrenaline released from nerve endings of the postganglionic neurons of the sympathetic division.
- **α_2- и β_2**- receptors are extrasynaptic, and are also available on the presynaptic membrane of the same neurons. On the α2-receptors act as adrenaline and noradrenaline. β2-receptors are sensitive mainly to adrenaline. A2-receptors on the presynaptic membrane noradrenaline acts on the principle of negative feedback - inhibits proper selection .
- **α_1** — localized in arterioles, stimulation leads to a spasm of arterioles, increasing the pressure, decrease vascular permeability and a decrease in exudative inflammation.
- **α_2** — mainly presynaptic receptors are "negative feedback loop" for the adrenergic system and their stimulation leads to lower blood pressure
- **β_1** — localized in the **heart,** the stimulation frequency leads to an increase (positive chronotropic effect) and force of cardiac contractions (positive inotropic effect) in addition**, increases the myocardial oxygen consumption and increase blood pressure**. It is also localized in the kidneys, being receptors juxtaglomerular apparatus.
- **β_2** — located in the **bronchioles**, the stimulation causes dilation of the bronchial tubes and the removal of bronchospasm. These receptors are found on cells of the liver, the effects on them hormone causes **glycogenolysis** and glucose output in blood.
- **β_3** — located in the adipose tissue. Stimulation of these receptors enhances lipolysis and leads to the release of energy and to increase heat production



- Механизм действия адренергических рецепторов. Эпинефрин и норадреналин являются лигандами для адренергических рецепторов α_1, α_2 или β. С α_1-адренергическим рецептором связывается α-субъединица G_q, что приводит к повышению внутриклеточной концентрации ионов кальция и, например, к сокращению гладкой мускулатуры. С α_2-адренергическим рецептором α_2 связывается α-субъединица G_i, что приводит к снижению концентрации цАМФ или, например, к сокращению гладкой мускулатуры. С β-рецептором связывается α-субъединица G_s, что приводит к повышению внутриклеточной концентрации цАМФ и, например, к сокращению сердечной мускулатуры, расслаблению гладкой мускулатуры и гликогенолизу.

GPCR and Diseases

- Obesity
- Cardiovascular Disease
- Inflammation
- Cancer
- Diabetes
- Alzheimer's Disaese



Thank you for attention!!!