

CHAPTER 02 — CELL COMMUNICATION AND SIGNALING

Membrane Receptors

Definition: Membrane receptors are transmembrane glycoproteins with three regions: an extracellular glycosylated region that recognizes and binds the molecule; a transmembrane hydrophobic region anchored in the membrane; and an intracellular region responsible for biochemical events.

Classification of membrane receptors

- Ion-channel receptors, which transduce the signal themselves.
- Enzyme receptors, which transduce the signal themselves.
- Receptors coupled to distinct effectors, which require the intervention of other proteins for signal transduction.

Classification des récepteurs membranaires

Récepteurs canaux-ioniques, transduisant eux-mêmes le signal ;

Récepteurs enzymes, transduisant eux-mêmes le signal ;

Récepteurs couplés à des effecteurs distincts, nécessitant l'intervention d'autres protéines pour la transduction du signal.

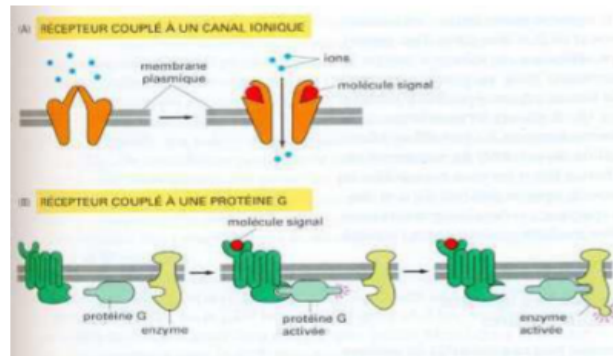


Figure 1. Different types of membrane receptors.

II.1. Ion-channel receptors

These are transmembrane proteins responsible for transmembrane ionic equilibria involved in the rapid transmission of signals across the synapse between two electrically excitable cells, such as neurons or muscle cells.

These receptors possess ligand-binding sites with a hydrophobic anchoring region in the membrane delimited by the subunits.

This type of transmission involves neurotransmitters as informational molecules.

II.1. Ion-channel receptors (continued)

(Examples: ATP, glutamate, glycine, acetylcholine, or serotonin).

Cation passage → **Depolarization** → **Activation** (a positively charged ion is an ion that has lost one or more electrons).

Anion passage → **Polarization** → **Inhibition** (an anion carries a negative charge).

II.1.1. An activating receptor: the nicotinic acetylcholine receptor

It functions as a non-selective cation channel that allows Na^+ and Ca^{2+} to enter and K^+ to leave. It is located on the motor end plates of neuromuscular junctions. Its agonist is nicotine, and its antagonist is curare.

It contains five different protein subunits, each possessing four transmembrane segments. These subunits are: two α subunits, one β , one δ , and one ϵ . The COOH and NH₂ parts of the α subunits are extracellular. The α subunits contain the acetylcholine-binding sites.

laissant sortir K^+ . Il est localisé sur les plaques motrices des jonctions neuromusculaires. Son agoniste est la nicotine, son antagoniste est le curare. Il comporte 5 sous-unités protéiques différentes possédant chacune 4 segments transmembranaires. Ces sous-unités sont : 2 α , une β , une δ , une ϵ . Les parties COOH et NH₂ des sous-unités α sont extracellulaires. Ce sont les sous-unités α qui comportent les sites de liaison de l'acétylcholine (Fig. 8).

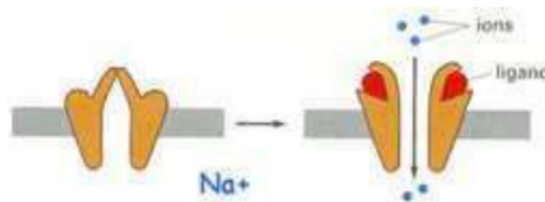


Figure 2. Nicotinic acetylcholine receptor.

II.1.2. Inhibitory anion receptor: the GABA receptor

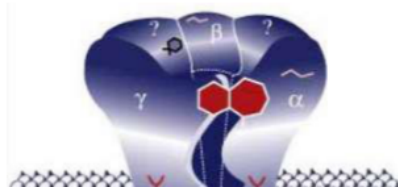
- It is a selective anion channel that allows Cl^- to enter.
- Binding of GABA to its recognition site causes a chloride (Cl^-) channel to open.

II.1.2. Inhibitory anion receptor: the GABA receptor (continued)

- The opening of the Cl^- channel allows Cl^- ions to enter and produces hyperpolarization of the target cell.
- It is expressed in the central nervous system (CNS).
- Its agonists include benzodiazepines such as Valium.
- Most benzodiazepines (BZD) facilitate opening of the Cl^- channel by GABA and therefore have an inhibitory effect.
- Its basic structure is close to that of the nicotinic receptor: five protein subunits, each presenting four transmembrane segments (M1 to M4).
- Several types of GABA receptors exist, differing in their subunits. Seven types of subunits are possible: α , β , γ , δ , π , ρ , ϵ .

chlore (Cl^-) qui laisse entrer les ions Cl^- et produit l'hyperpolarisation de la cellule cible.

- Il est exprimé au niveau du SNC.
- Ses agonistes sont les benzodiazépines dont le valium.
- La plupart des benzodiazépines (BZD) favorisent l'ouverture du canal Cl^- par le GABA et ont donc un effet inhibiteur
- La structure de base est proche de celle du récepteur nicotinique : cinq sous-unités protéiques, chacune présentant 4 segments transmembranaires (M1 à M4).



GABA receptor structure.

II.1.2. Enzyme receptors

These transmembrane proteins exist as monomers, dimers, or tetramers. They possess a single transmembrane domain. The NH_2 end is located in the extracellular receptor region and the COOH end is located intracellularly. They have a dual function of signal recognition and effector activity.

Their cytosolic domain has intrinsic enzymatic activity, which induces a cascade of phosphorylations of membrane or cytosolic proteins. According to the enzymatic activity of their cellular region, three families are distinguished:

- Receptors with tyrosine kinase activity.
- Receptors with serine-threonine kinase activity.
- Receptors with guanylate cyclase activity.

II.1.2.1. Receptors with tyrosine kinase activity

Two examples should be known: receptors for several growth factors and the insulin receptor (and therefore also the receptors for IGF: insulin-like growth factor). These include growth factors associated with fibroblasts (FGF), endothelial cells (VEGF), platelet-derived growth factor (PDGF), epithelial cells (EGF), and insulin.

Binding of two ligand molecules induces receptor dimerization (except for the insulin receptor), followed by receptor autophosphorylation. The phosphorylated receptor can then recruit associated proteins, phosphorylate several target proteins, and induce phosphorylation–dephosphorylation cascades that regulate the function of downstream proteins.

La fixation de deux molécules de ligand induit la dimérisation du récepteur (sauf pour le récepteur de l'insuline), suivi par l'autophosphorylation du récepteur qui devient capable de recruter des protéines associées, de phosphoryler plusieurs protéines cibles et d'induire des cascades de phosphorylation-déphosphorylation qui régulent la fonction de la protéine en aval

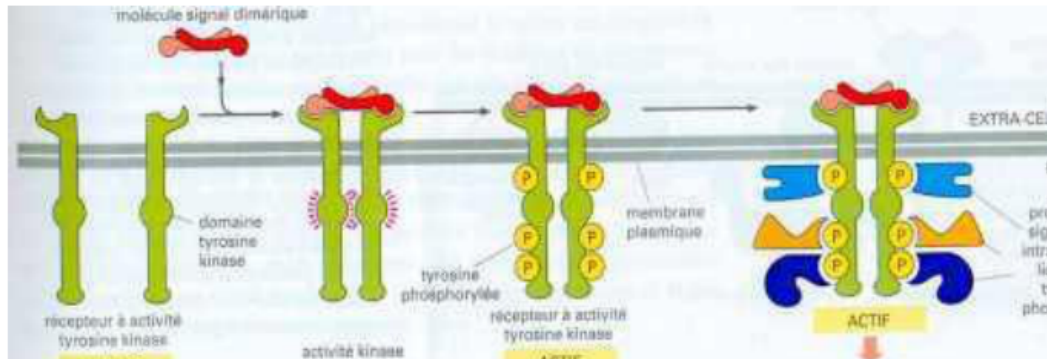


Figure 3. Activation of receptors with tyrosine kinase activity.

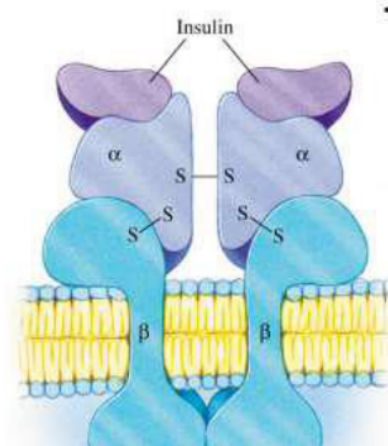
Tyrosine-kinase receptors activate the monomeric G proteins Ras through an intermediate protein that is phosphorylated by the receptor. This protein stimulates the exchange of GDP for GTP on Ras. Activated Ras (Ras coupled to GTP) induces a cascade of phosphorylations. The final kinases in the cascade belong to the MAP kinase family (Mitogen-Activated Protein Kinases). The reaction cascade leads to modification of the activity of cytosolic proteins that are translocated into the nucleus and modify gene expression.

Insulin receptor — Structure

Insulin receptor — Structure

- A tetramer formed by two extracellular α chains linked by disulfide bonds to two transmembrane β chains.
- The α subunits are extramembranous and allow insulin binding.
- The transmembrane β subunit contains a tyrosine kinase activity domain in its intracellular region, responsible for signal transduction.

activité tyrosine kinase dans son domaine intracellulaire
responsable de la transduction du message.



Insulin receptor structure.

Mechanism of action

- Binding of insulin to the α subunits causes a change in spatial conformation.
- Activation of the kinase domain of the two β subunits.
- The tyrosine residues of the β subunits are then phosphorylated (autophosphorylation).
- The phosphorylated receptor recruits a receptor-substrate protein and phosphorylates it.
- This triggers a cascade of biochemical events leading to the response (rapid response).

II.1.2.2. Receptors with serine-threonine kinase activity

Here again, the tetramer is formed by four transmembrane subunits (two types: RI and RII), each having serine-threonine kinase activity. The same phenomenon of autophosphorylation of the intracellular regions is observed, followed by phosphorylation of protein transcription factors (Fig. 4).

protéiques de transcription (Fig. 04).

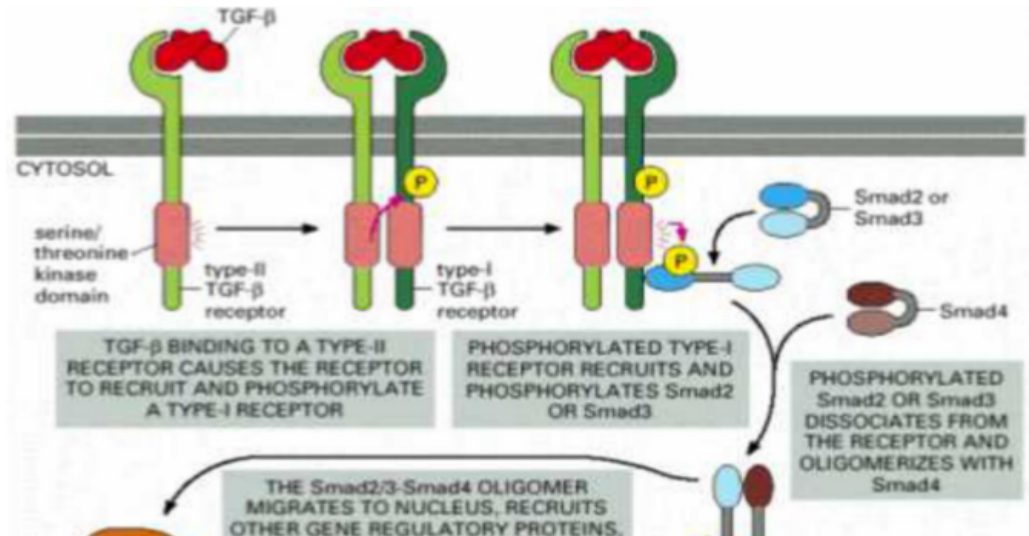


Figure 4. Receptors with serine-threonine kinase activity.

II.1.2.3. Receptors with guanylate cyclase activity

Examples: TGF and BMP receptors...

Binding of the ligand to this enzyme-receptor causes the formation, from guanosine triphosphate (GTP), of cyclic guanosine monophosphate (cGMP), which activates specific protein kinases (PKG).

II.1.2.3. Receptors with guanylate cyclase activity (continued)

Receptors with guanylate cyclase activity are receptors for natriuretic peptides. They are transmembrane homodimers. Intracellular activation of guanylate cyclase by binding of the peptide extracellularly induces synthesis of the second messenger cyclic GMP (guanosine-3',5'-monophosphate) from GTP (Fig. 13).

End of Chapter 02