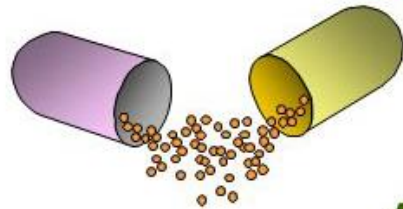


INTERACTION DRUG \Leftrightarrow BODY

What the drug does to the body

Pharmacodynamics, PD

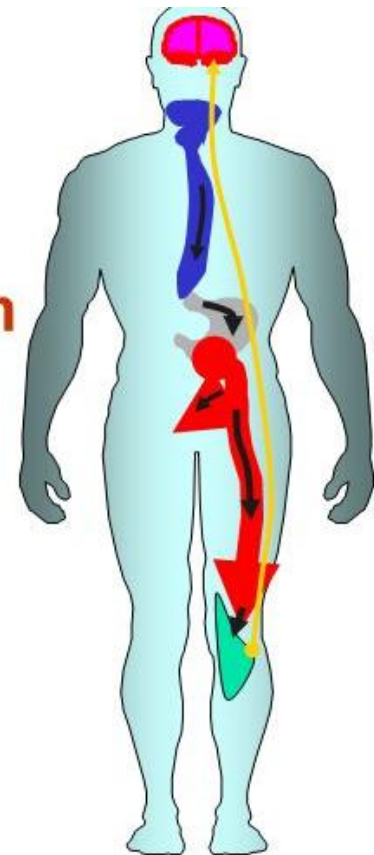
Drug Action and Mechanism



**Absorption, Distribution,
Metabolism, Excretion**

Pharmacokinetics, PK

What the body does to the drug



PHARMACODYNAMICS

Receptors

- intracellular receptors
- membrane receptors
 - *Channel receptors*
 - *G protein-coupled receptors*
 - *Tyrosine-kinase receptors*

Drug/receptor interactions

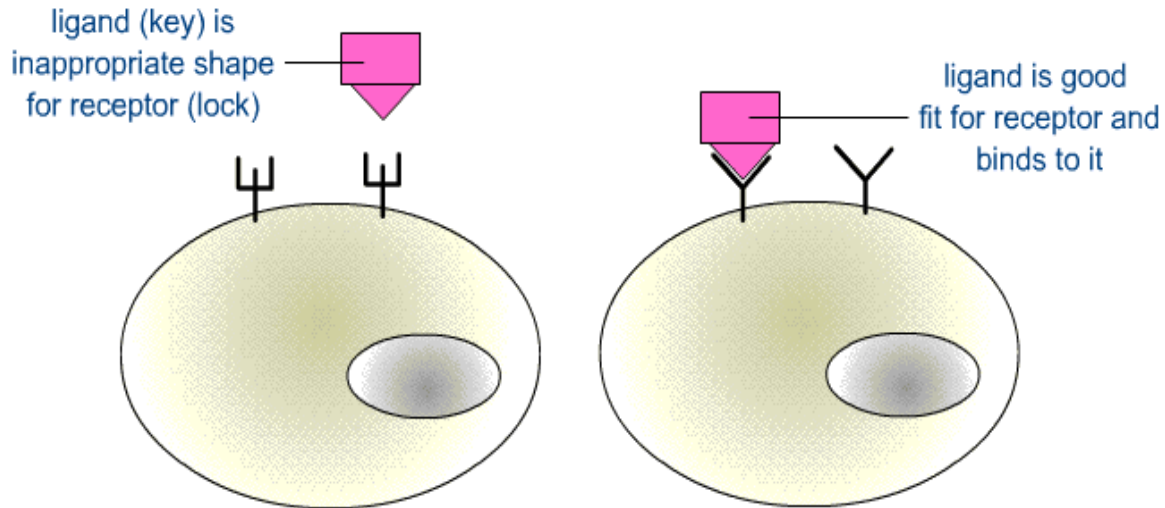
- agonists and antagonists
- potency and efficacy (effectiveness)
- therapeutic index

Drug effects

- therapeutic effects
- side effects
- toxic effects

PRINCIPLES OF CELL SIGNALING

Cells are communicating with each other by releasing soluble factors able to recognize and bind to their target cells. Target cells possess appropriate **receptors** to trigger the specific response mediated by hormones, neurotransmitters and soluble mediators. In general, a molecule able to bind to a receptor is called **ligand**.



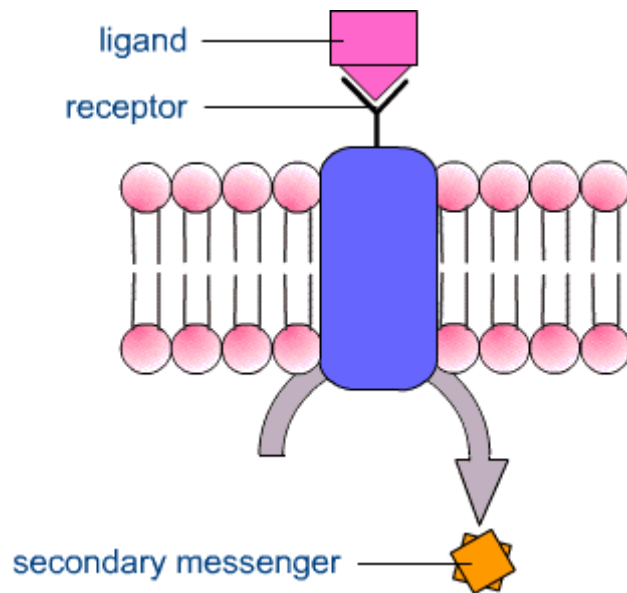
*Most signal molecules are **hydrophilic** and are therefore unable to cross the target cell's plasma membrane directly; instead, they bind to cell-surface receptors, which in turn generate signals inside the target cell.*

*Some small signal molecules, by contrast, diffuse across the plasma membrane and bind to receptor proteins inside the target cell—either in the cytosol or in the nucleus. Many of these small signal molecules are hydrophobic (**lipophilic**) and poorly soluble in aqueous solutions; they are therefore transported in the bloodstream and other extracellular fluids bound to carrier proteins, from which they dissociate before entering the target cell*

RECEPTOR

The receptor is a regulatory macromolecule whose structure is complementary to a ligand, as well as a lock is complementary to a key

Drug should have – **selectivity** to a receptor
Receptor should have - **ligand specificity** to elicit action.



DRUG RECEPTOR INTERACTIONS

Effect of drug is attributed to two factors:

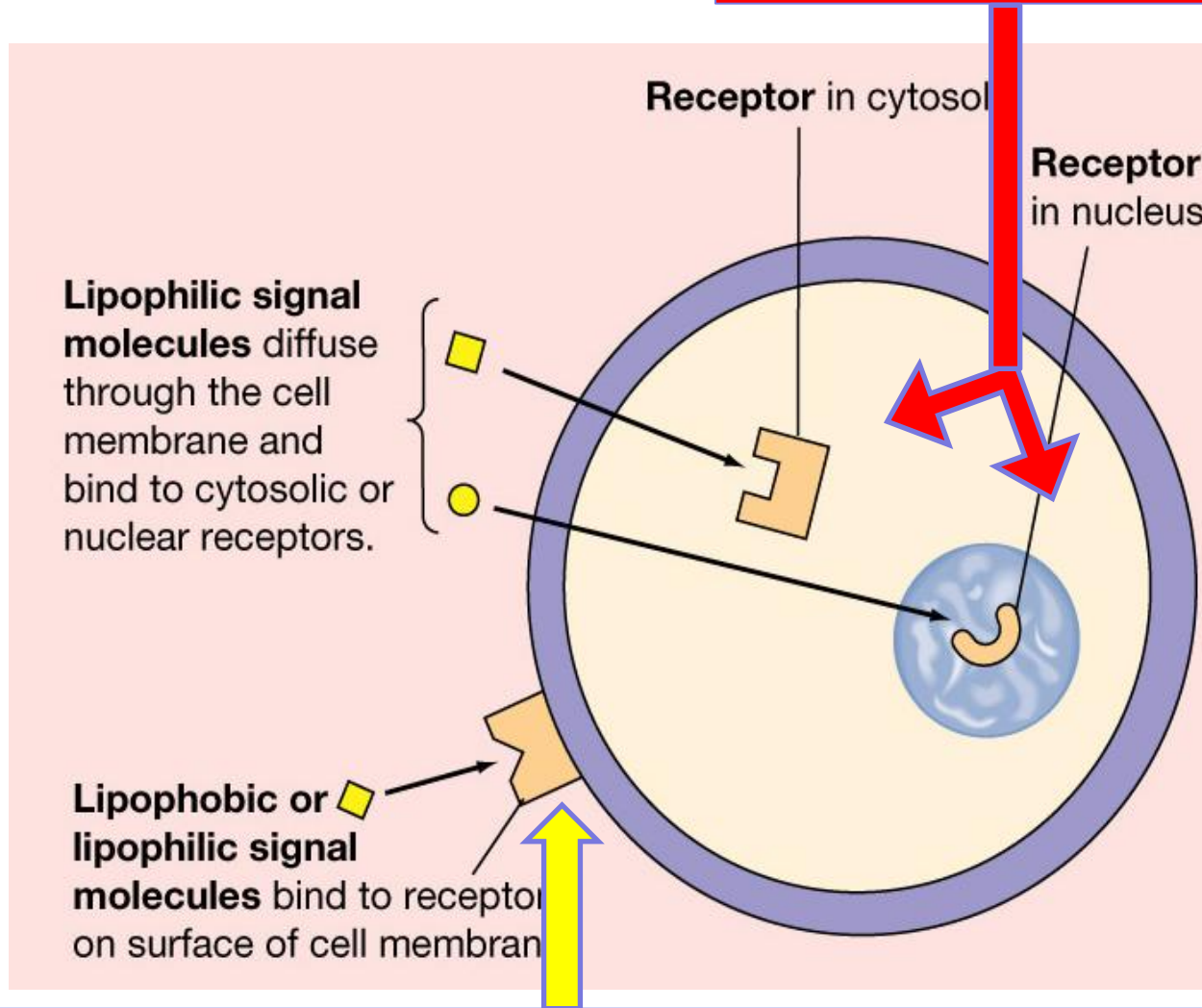
Affinity: tendency of the drug to bind to receptor and form D-R complex .

Efficacy or intrinsic activity: ability of the drug to trigger pharmacological responses after forming D-R complex

The ligand/receptor binding triggers a conformational change responsible for its biological effect

RECEPTORS: CELLULAR LOCALIZATION

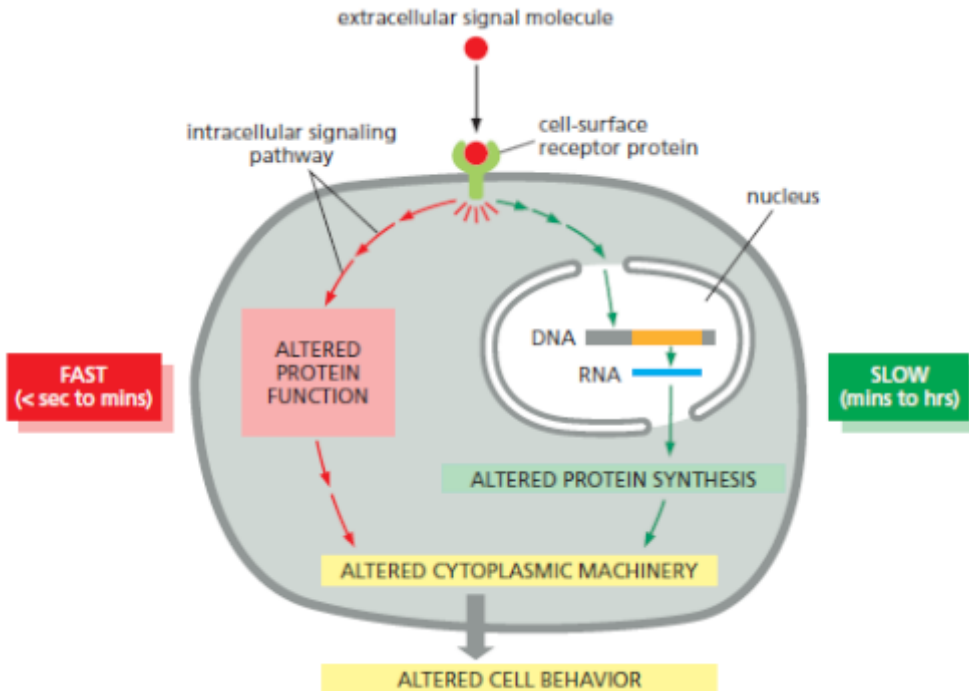
INTRACELLULAR RECEPTORS



MEMBRANE RECEPTORS – CELL SURFACE RECEPTORS

TIME TO BIOLOGICAL RESPONSE

The speed of any signaling response depends on the nature of the intracellular signaling molecules that carry out the target cell's response.



When the response requires only changes in proteins already present in the cell, it can occur very rapidly:

- an allosteric change in a neurotransmitter-gated ion channel, for example, can alter the plasma membrane electrical potential in **milliseconds**.

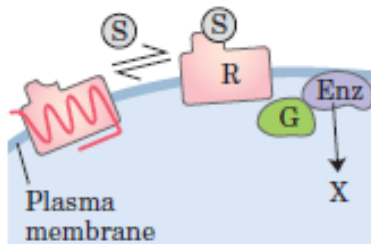
- responses that depend solely on protein phosphorylation can occur within **seconds**.

- when the response involves changes in gene expression and the synthesis of new proteins, however, it usually requires many **minutes** or **hours**, regardless of the mode of signal delivery.

SIX BASIC RECEPTOR TYPES

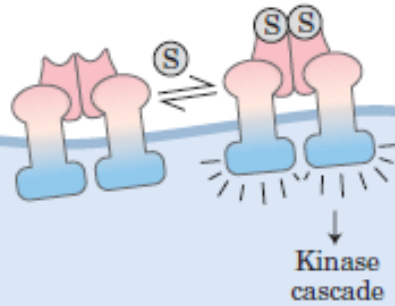
G protein-coupled receptor

External ligand (S) binding to receptor (R) activates an intracellular GTP-binding protein (G), which regulates an enzyme (Enz) that generates an intracellular second messenger, X.



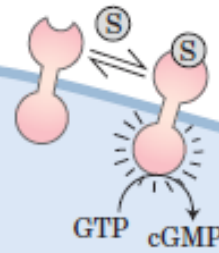
Tyrosine kinase receptor

Ligand binding activates tyrosine kinase activity by autophosphorylation.



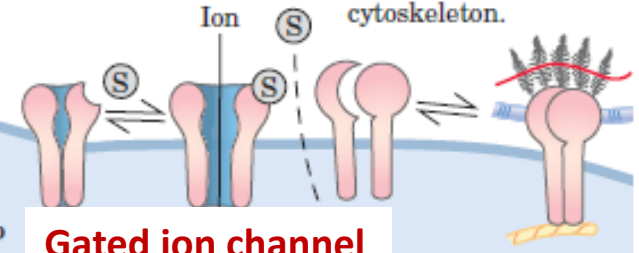
Guanylyl cyclase receptor

Ligand binding to extracellular domain stimulates formation of second messenger cyclic GMP.



Adhesion receptor (integrins)

Binds molecules in extracellular matrix, changes conformation, thus altering its interaction with cytoskeleton.



Nuclear envelope

DNA

mRNA

Protein

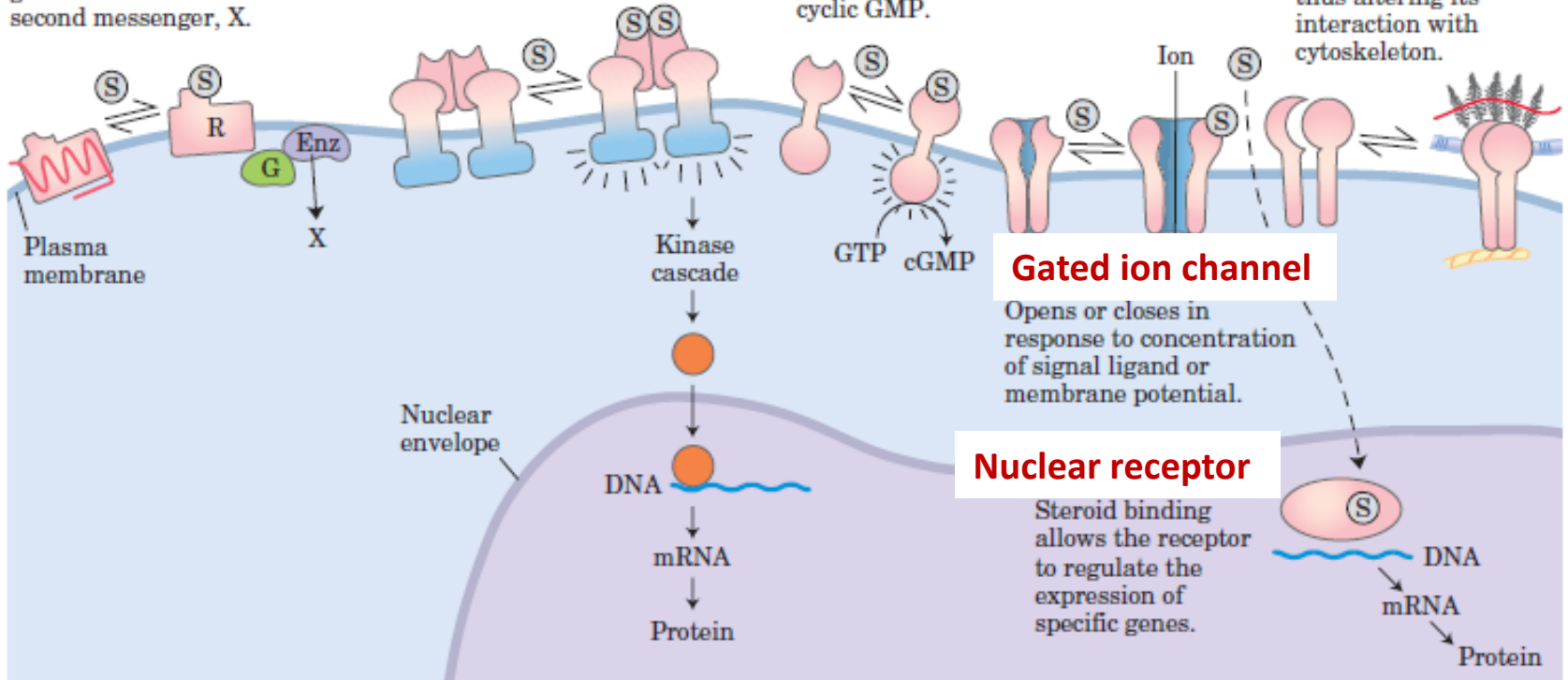
Nuclear receptor

Steroid binding allows the receptor to regulate the expression of specific genes.

DNA

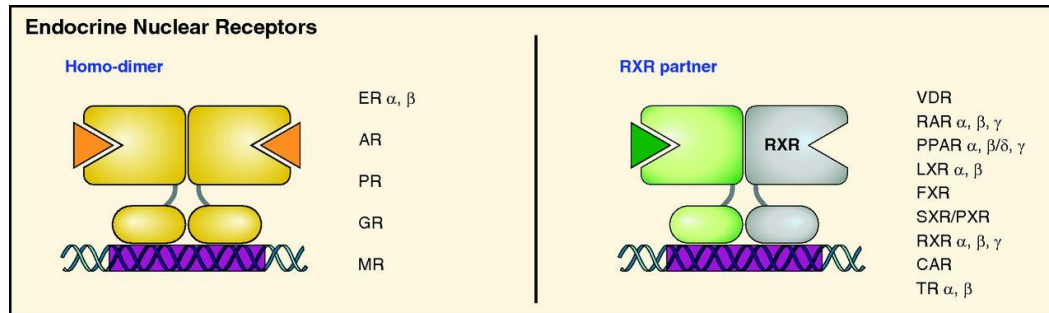
mRNA

Protein

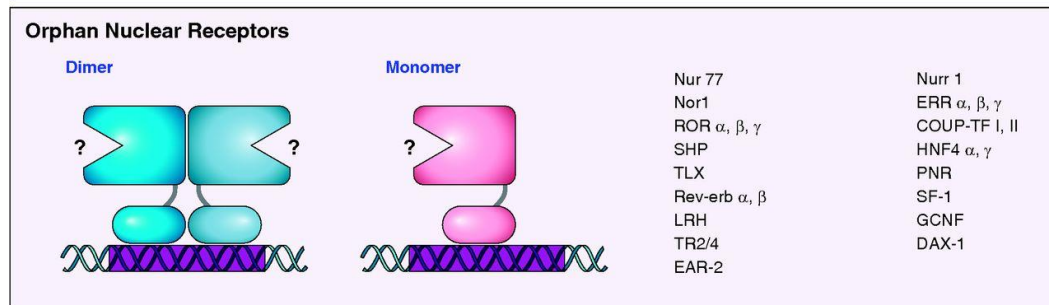


NUCLEAR RECEPTORS (NR) SUPERFAMILY

1. Endocrine receptors (ligands identified)



2. Orphan receptors (unknown ligands)



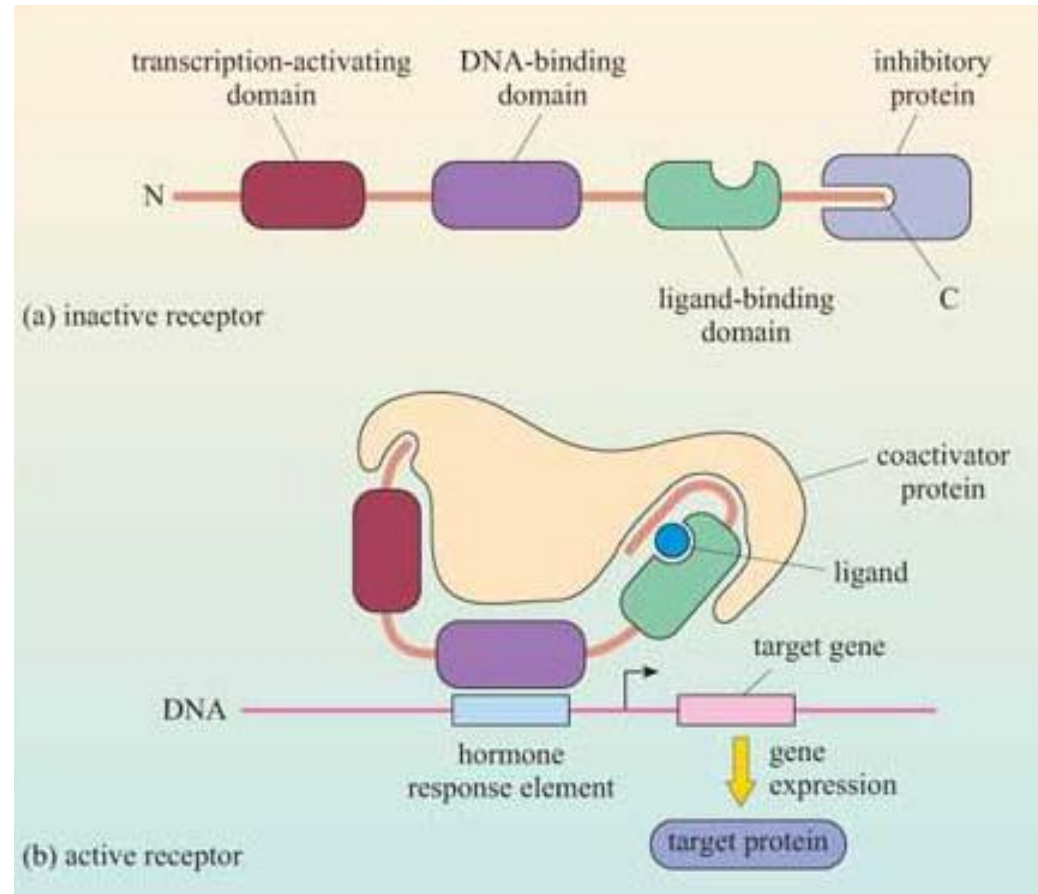
- NR superfamily members are divided into two main groups depending on the identification of endogenous ligands.
- NRs for which specific cognate ligands have been identified are known as endocrine NRs (top panels). NRs of this group bind to specific DNA elements as homodimers (top left) or heterodimers with RXR (top right).
- The other group is referred to as orphan NRs, for which endogenous ligands remain unknown (bottom panels).

NUCLEAR RECEPTORS

All nuclear receptors are structurally similar and present:

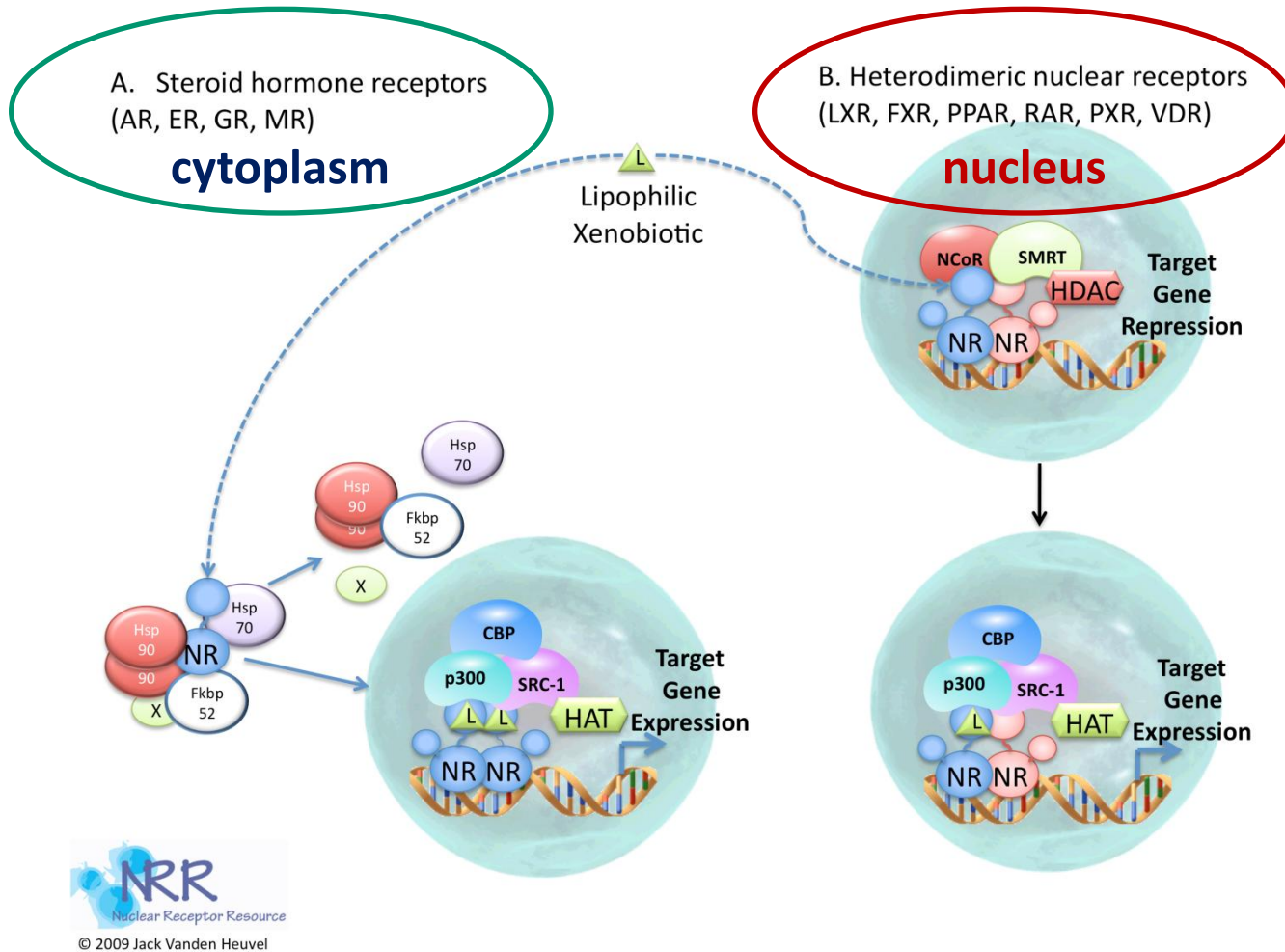
- a **TRANSCRIPTION-ACTIVATING DOMAIN**,
- a **DNA-BINDING DOMAIN** and
- a **LIGAND-BINDING** domain.

- *The receptors are usually held in an inactive conformation by inhibitory proteins.*
- *Binding of the ligand induces a conformational change that causes the inhibitory protein to dissociate from the receptor.*
- *The receptor–ligand complex is now able to bind to specific DNA sequences by means of its DNA-binding domain.*



The DNA sequence to which the receptor–ligand complex binds is a promoter region of the target genes; in the case of hormones, it is called a '**hormone response element (HRE)**'

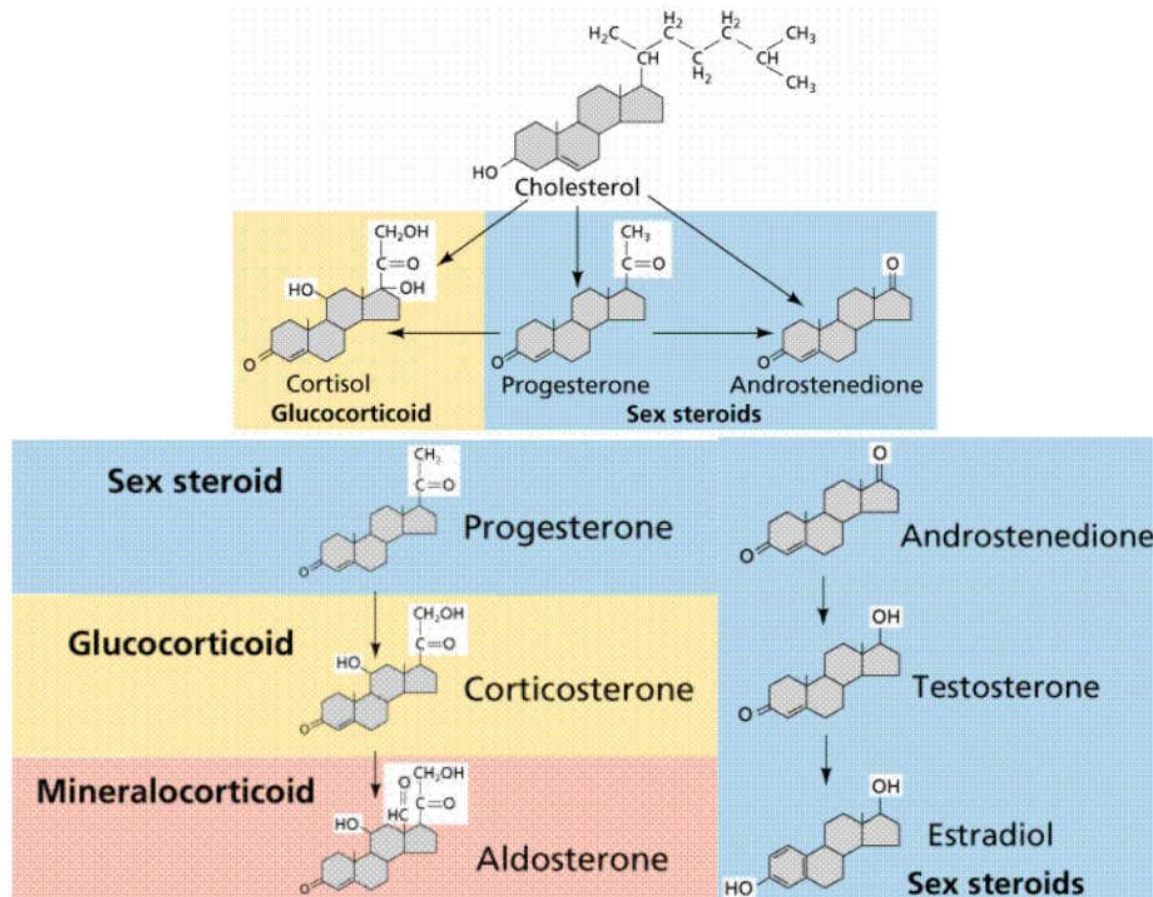
NUCLEAR RECEPTORS



Under resting conditions, NR localize either in the **cytoplasm** or in the **nucleus**. Mechanisms regulating their activation differs between cytoplasm or nuclear receptors

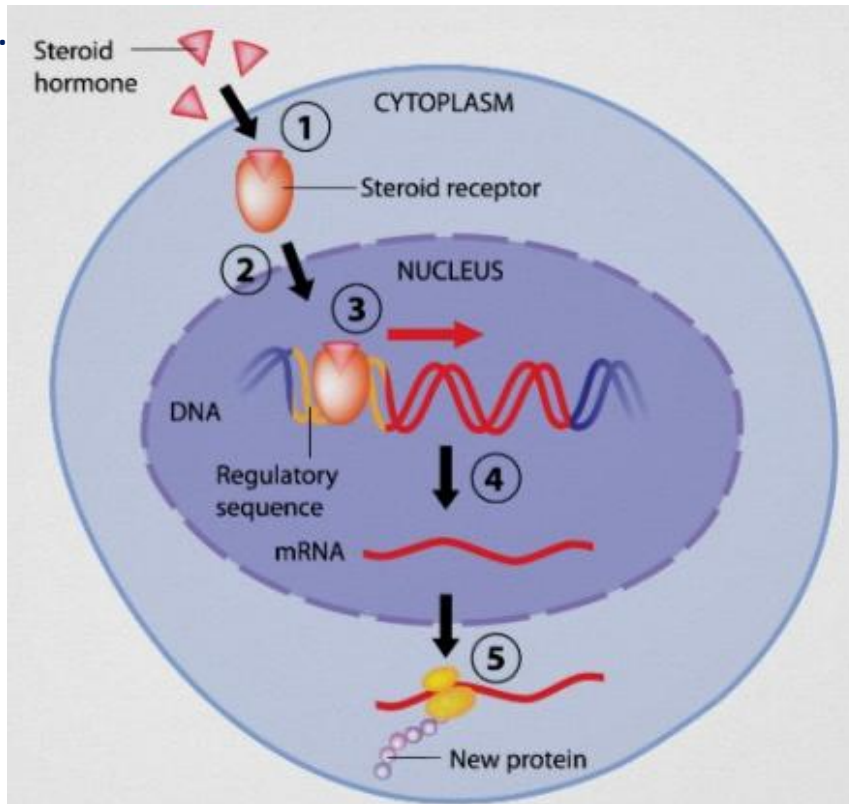
CLASS 1a: Steroid hormones receptors

LIGANDS: Steroid hormones share a common basic cholesterol structure. They all pass through the cell membrane to bind their cognate receptors **in the cytoplasm**.



CLASS 1a: Steroid hormones receptors

RECEPTORS: Steroid hormone receptors (SHR) are located **into the cytoplasm**.



- When the specific ligand binds to its receptor, the active H/R complex undergoes **dimerization** and then enters the nucleus to bind to specific genes

- The bound protein stimulates the transcription of the gene into mRNA

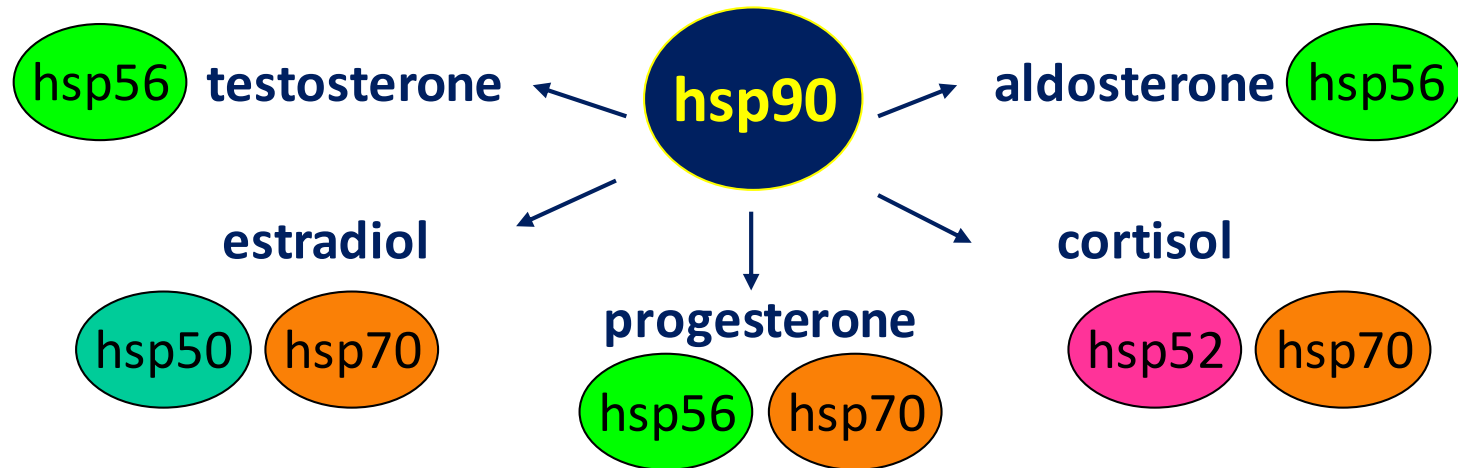
- The mRNA is translated into a specific protein

By regulating gene transcription processes, steroid hormone receptors are responsible for changes in cell structure and function.

Thus, although the activation of the L/R complex is fast, the subsequent biological/physiological response may require hours or days to become visible.

CLASS 1a: Steroid hormones receptors

REGULATORY MECHANISMS: The activity of a steroid hormone receptor (SHR) is tightly regulated: in the absence of the ligand, SHR are bound to inhibitory proteins known as **HEAT SHOCK PROTEINS (HSP)** which keep the receptor in the cytoplasm.

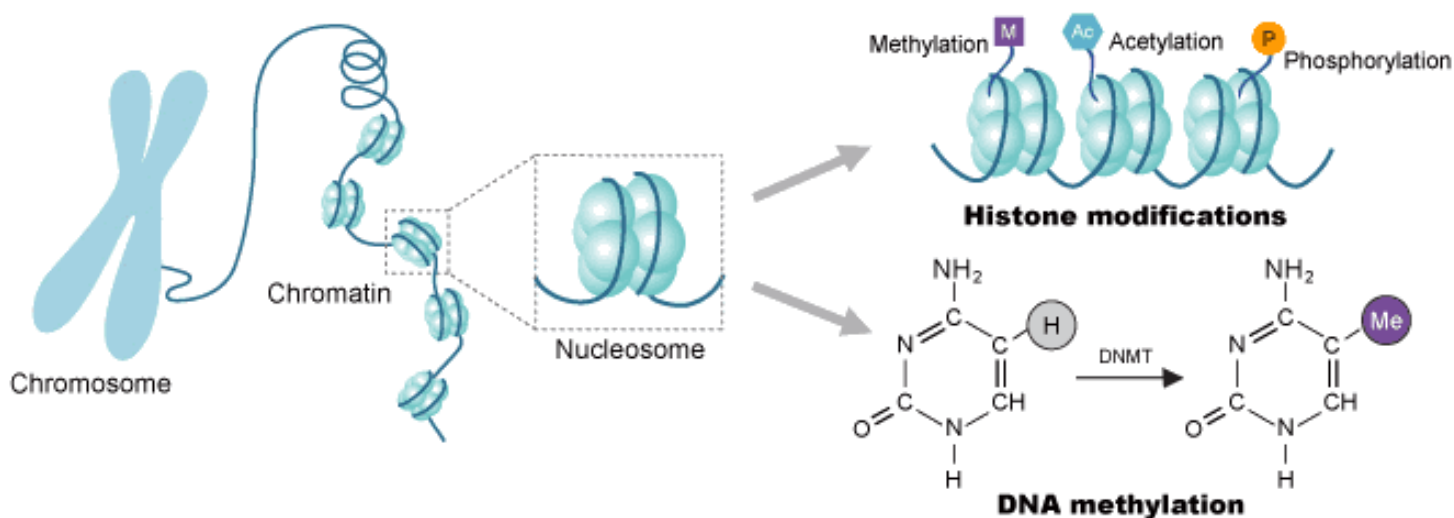


**When the specific ligand binds to a receptor,
the HSPs are released.**

CLASS 1a: Steroid hormones receptors

REGULATORY MECHANISMS: Beside the release of HSP, additional mechanisms ensure the signaling specificity. Once at the nuclear level, the ligand/receptor complex binds unique DNA sequences (**HORMONE RESPONSIVE ELEMENTS**) at the gene promoter. This binding, in turn, recruits **CO-ACTIVATORS** or **CO-REPRESSORS** able to facilitate or inhibit the transcription process.

These mechanisms involve, for example, methylation, acetylation or phosphorylation of histone proteins or DNA.



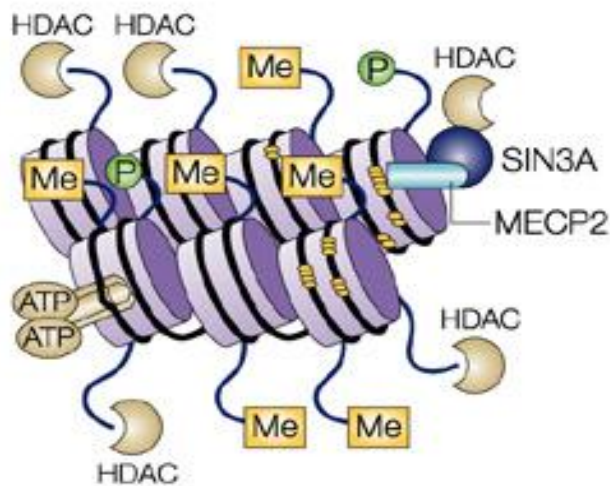
CLASS 1a: Steroid hormones receptors

REGULATORY MECHANISMS: acetylation/deacetylation of histone proteins

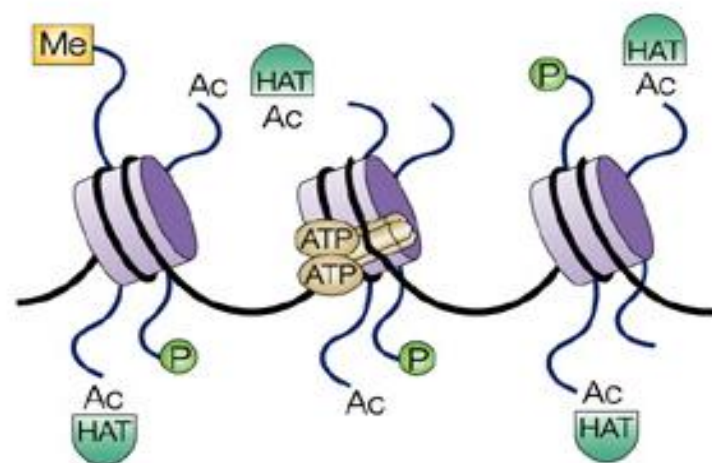
Histone deacetylases (HDAC) are enzymes that remove acetyl groups from a lysine on a histone, allowing the histones to wrap the DNA more tightly. In general, **histone deacetylation represses gene expression.**

Histone acetyltransferases (HATs) are enzymes that acetylate conserved lysine on histone proteins by transferring acetyl groups from acetyl CoA. In general, **histone acetylation increases gene expression.**

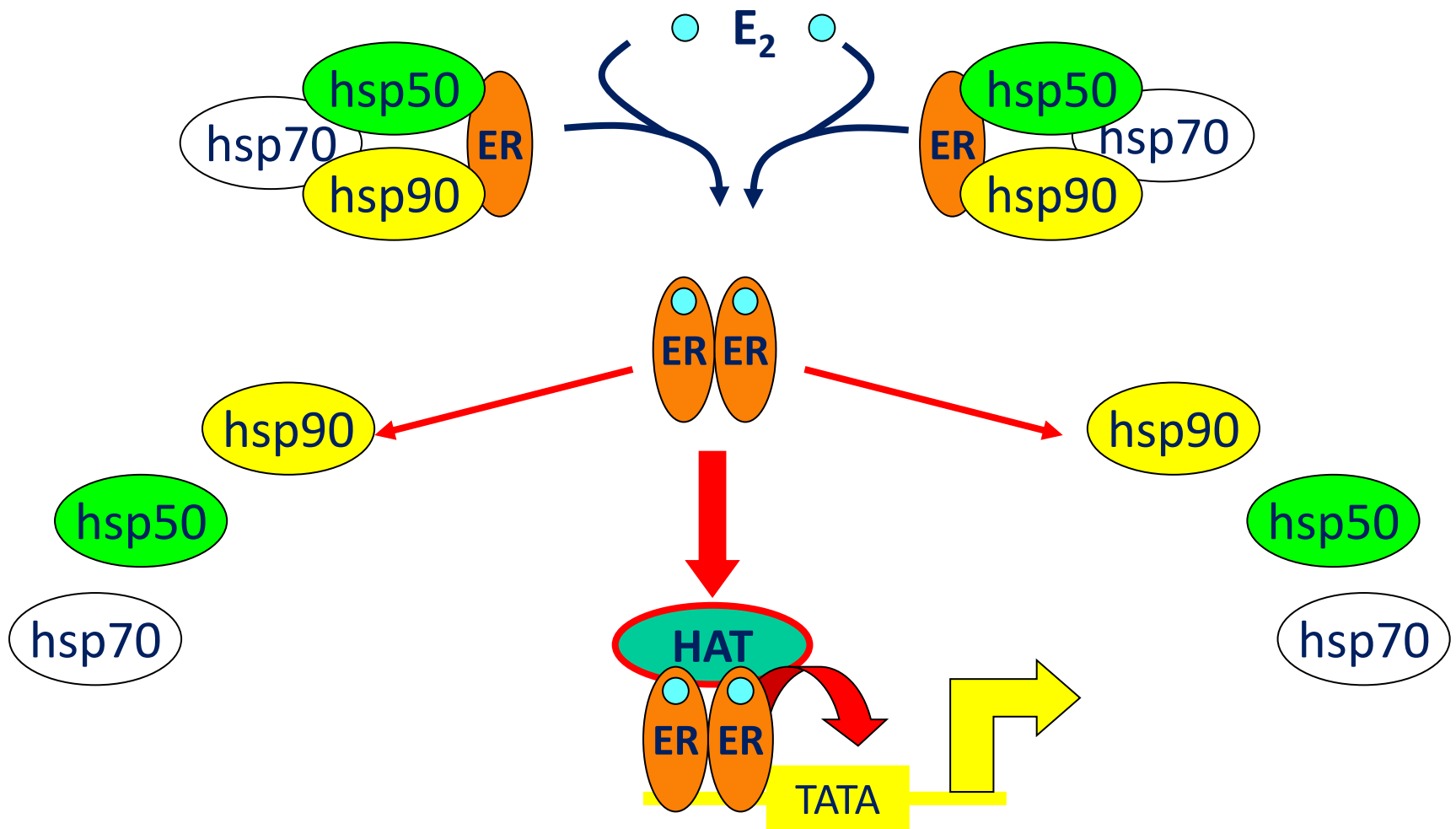
a Closed chromatin: transcriptional repression



b Open chromatin: transcriptional activation



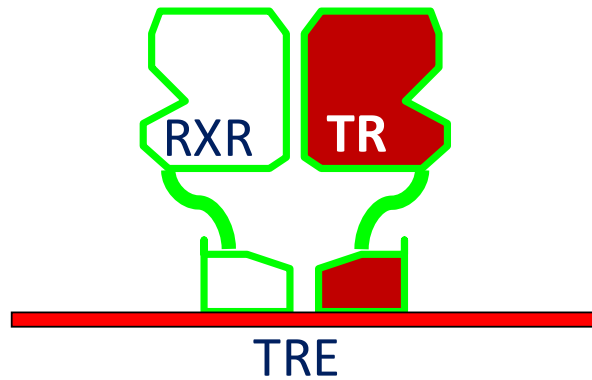
CLASS 1a: Activation of steroid hormones receptors



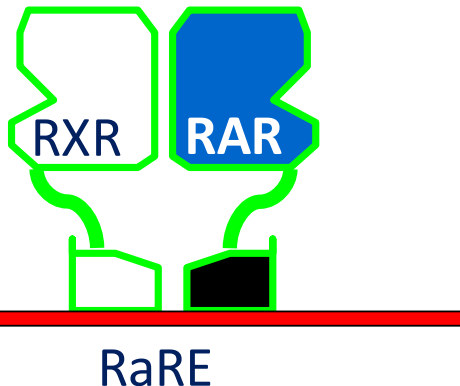
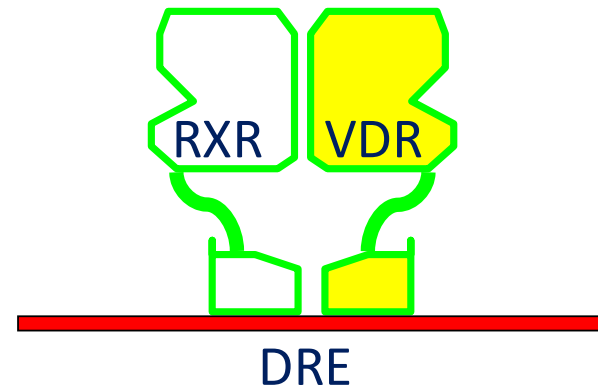
CLASS 1b: Non-steroid hormones receptors

Non-steroid hormone receptors are located **in the nucleus**. Under basal state, they are bound to DNA and are not active because linked to a **CO-REPRESSOR RXR** molecule.

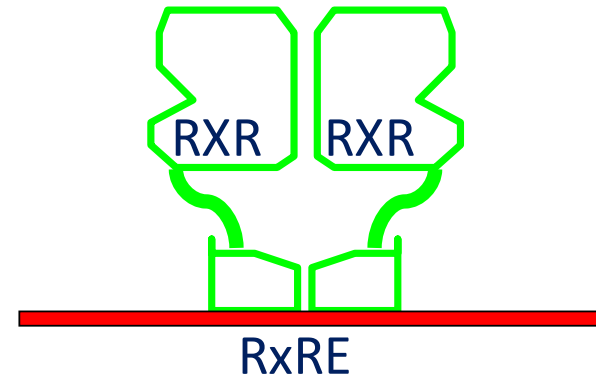
Thyroid hormone R



Activated Vitamin D R



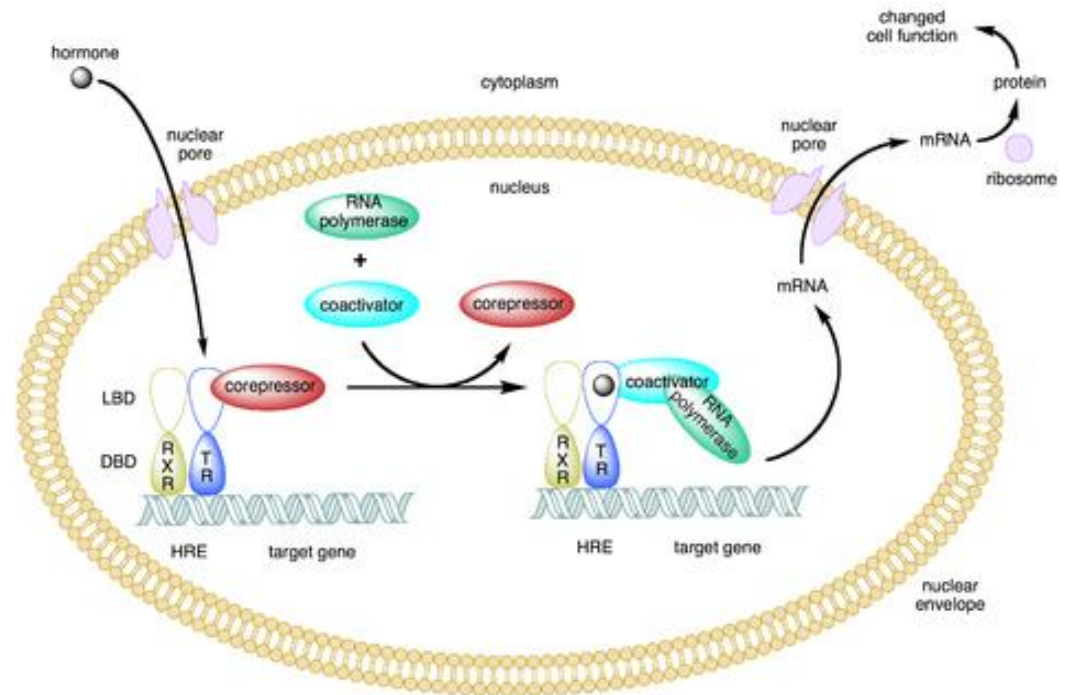
all-trans- retinoic acid R



9-cis- retinoic acid R

CLASS 1b: general concepts

- A Class Ib nuclear receptor (NR) is located in the nucleus bound to DNA, regardless of ligand-binding status.
- The thyroid hormone receptor (TR) heterodimerizes to the RXR.



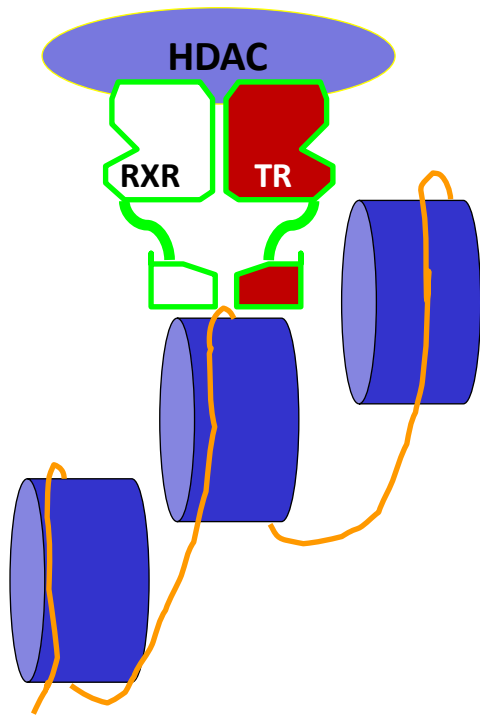
- In the absence of ligand, the TR is bound to **corepressor** protein.
- Ligand binding to TR causes a dissociation of corepressor and recruitment of coactivator protein, which, in turn, recruits additional proteins such as RNA polymerase that are responsible for transcription of downstream DNA into RNA and eventually protein, which results in a change in cell function.

CLASS 1b: Activation of NON steroid hormones receptors

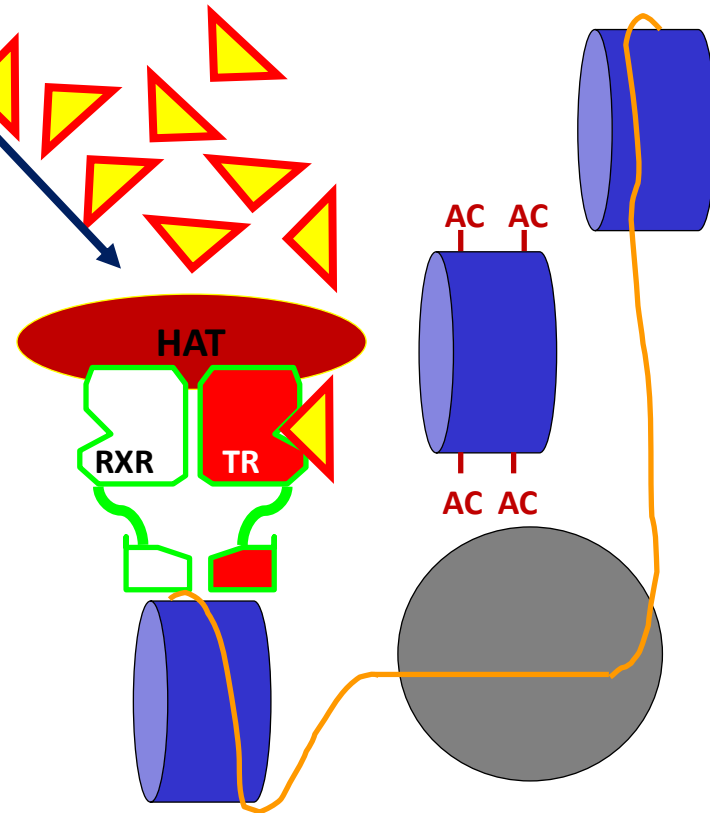
Transcriptional Repression

Transcriptional Activation

+ Ligand (hormone)



Histone deacetylase
(HDAC)



Histone acetyl
transferase (HAT)

PEROXISOME-PROLIFERATING ACTIVATOR (PPAR) RECEPTORS

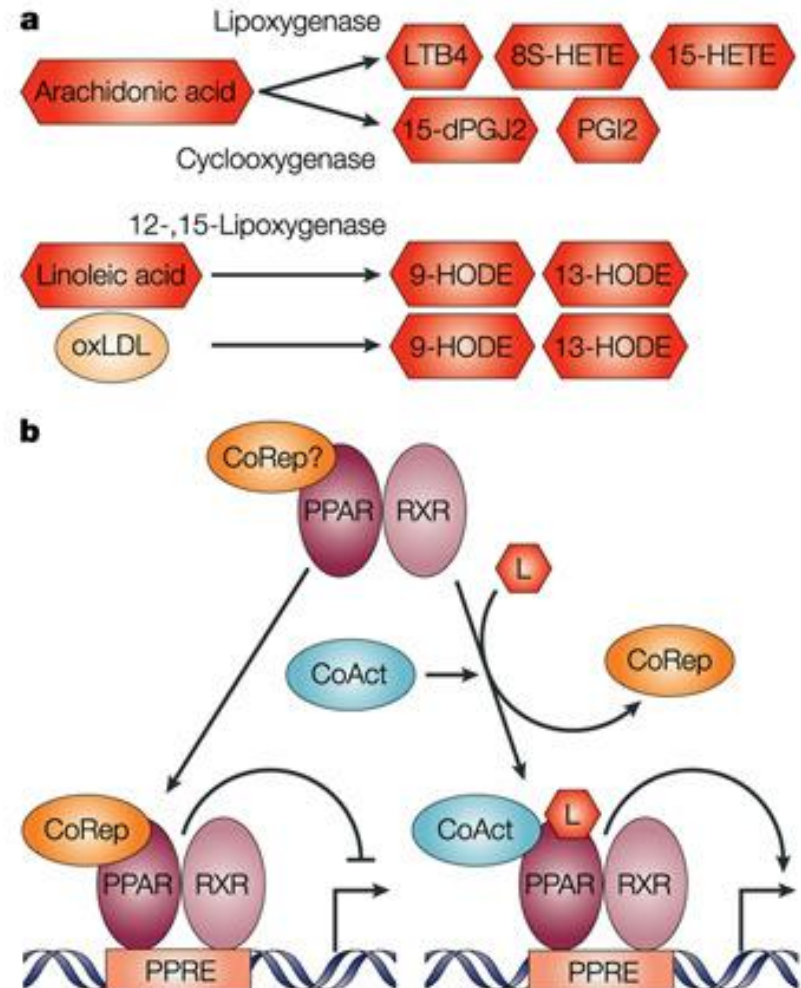
PPAR family of nuclear receptors plays a major regulatory role in the energy metabolism and metabolic function.

PPAR α is expressed in the liver, kidney, heart, muscle, adipose tissue and others.

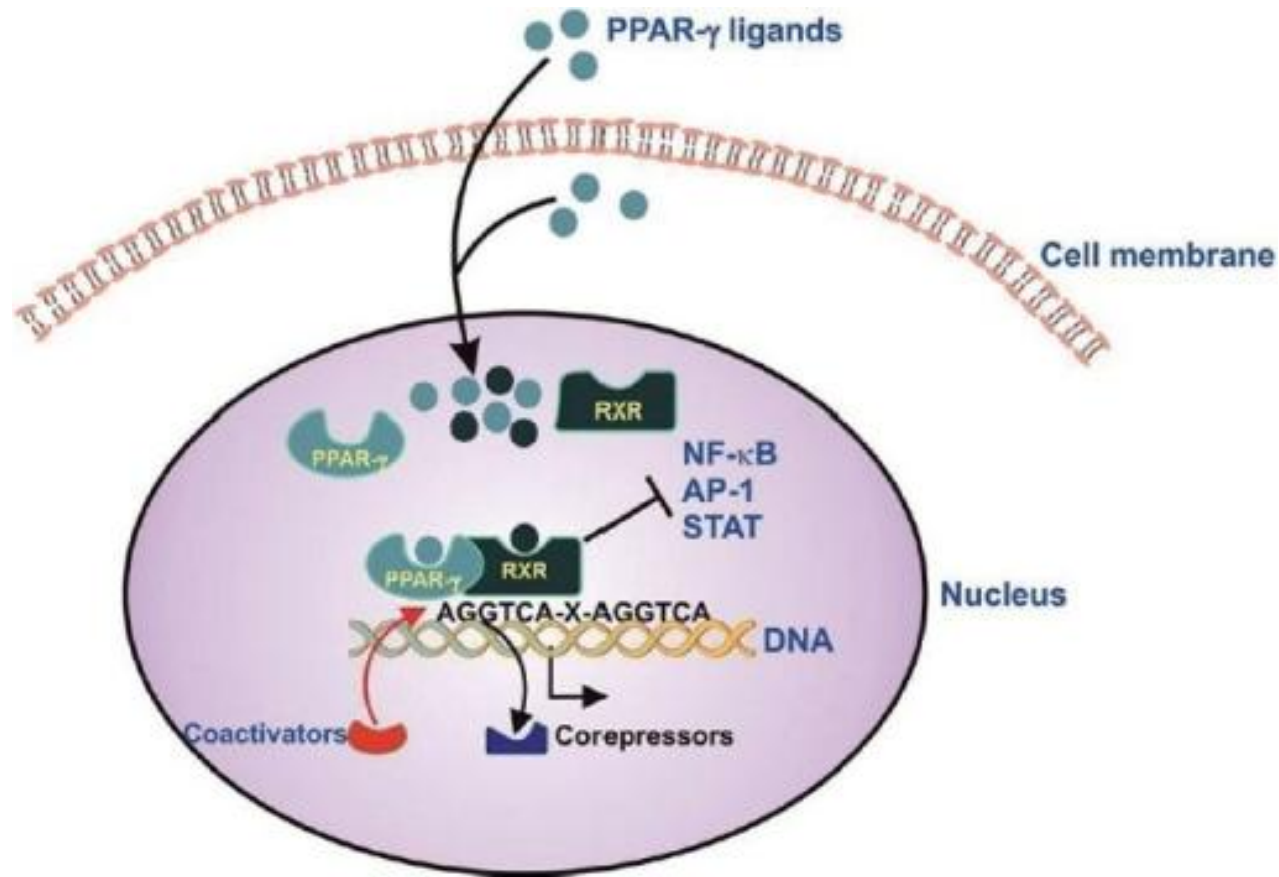
PPAR β/δ is expressed mainly in brain, adipose tissue and skin

PPAR γ is almost ubiquitous.

These nuclear receptors bind as heterodimers with the retinoid X receptor, RXR. Upon binding of ligand, they recognize specific sequences in the promoter of target genes (PPAR response elements), and activate transcription.



PEROXISOME-PROLIFERATING ACTIVATOR (PPAR) RECEPTORS



Pharmacological modulation of these receptors is involved in the treatment of metabolic diseases such as dislipidemia and insulin resistance conditions