كلية الطب البيطري – جامعة تكريت

ماجستير أدوية

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2024-2025 \ First Term

((6))

Advanced Pharmacology

RECEPTORS & SIGNALLING

https://youtu.be/WORIhbaRABg

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3. Kinase-linked receptors:

Are transmembrane receptors
Transduction takes minutes.
They play a role in cell division, cell growth, inflammation, tissue repair, apoptosis & immune responses.

Structure:
Extracellular ligand binding domain
Intracellular enzyme domain
A single transmembrane helix which links the outer domain to the inner domain

- **The main types:**

1. Receptor tyrosine kinases (RTK)
2. Serine/ threonine kinases
3. Cytokines receptors
4. Guanylate cyclase-linked receptor

1. **Receptor tyrosine kinase (RTK) :**

   Possess tyrosine kinase activity.

   e.g. growth factor, insulin receptors & toll-like receptor.

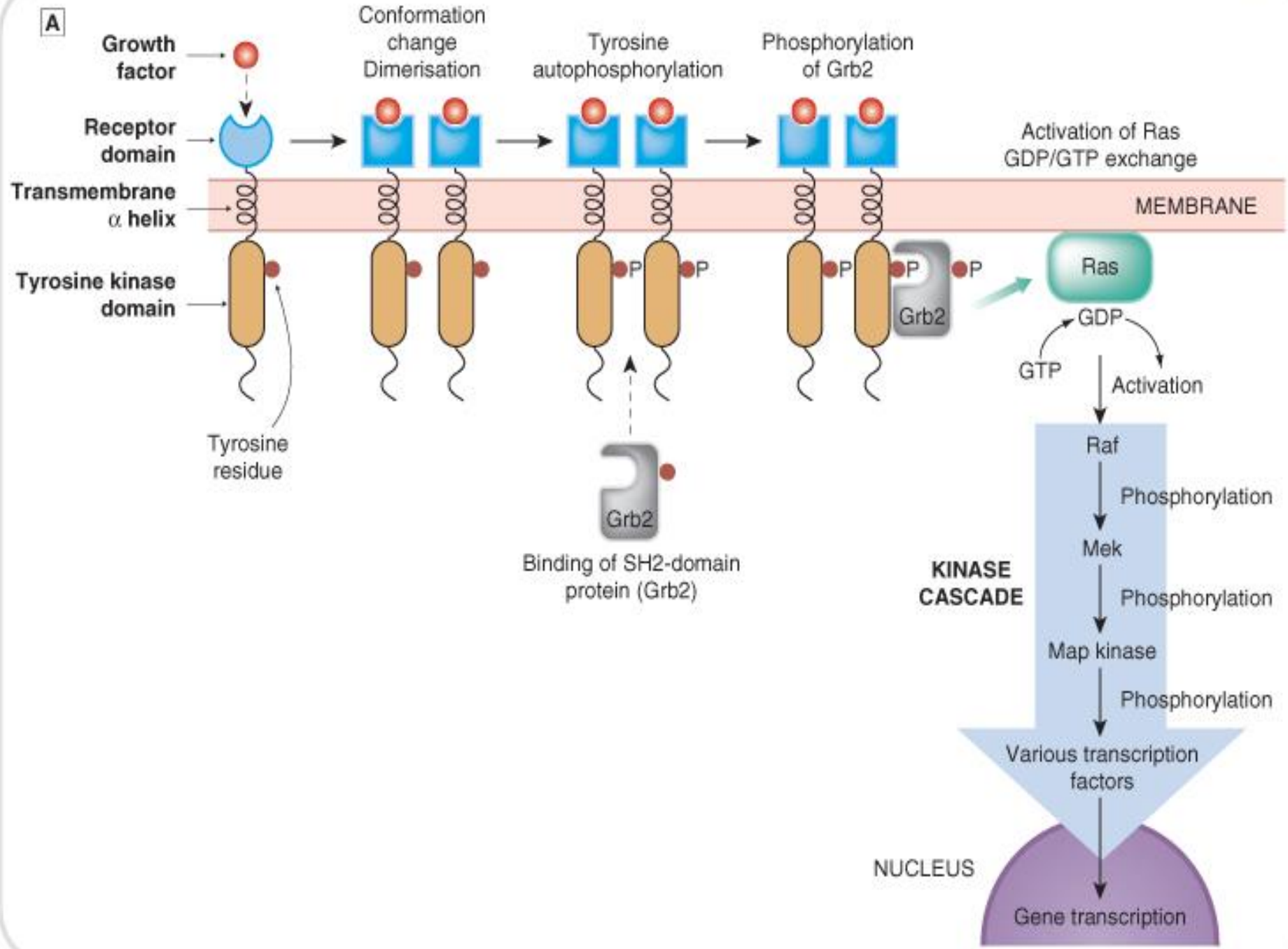
Signal transduction mechanism:

Occupation of the receptor, conformational change & dimerization

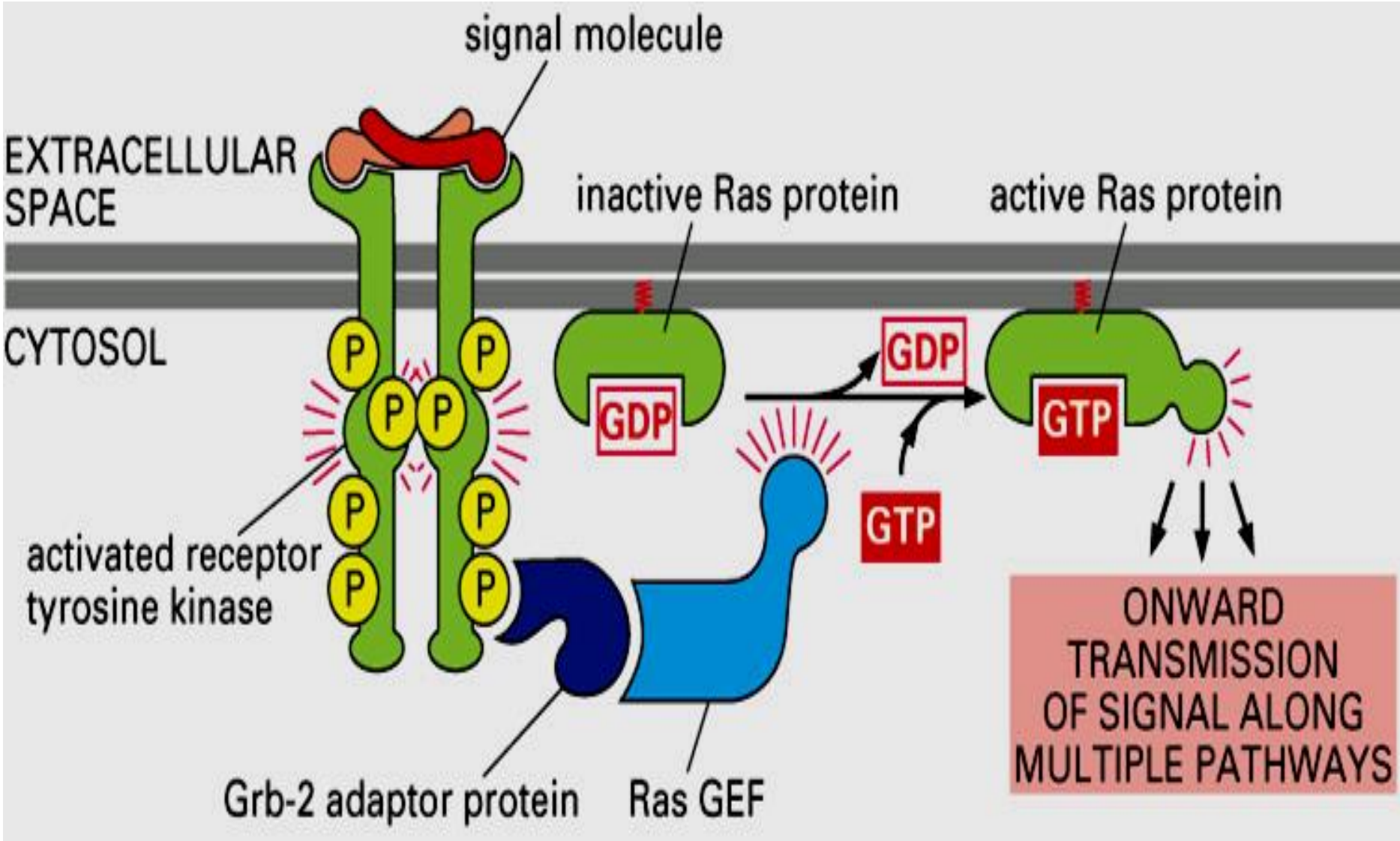
- Autophosphorylation of the tyrosine residue which phosphorylates “adapter protein” → activates Ras (GDP→ GTP) → activates Raf→ Mek → MAP kinase (mitogen activated protein) → gene transcription
- MAP kinase pathway play a role in cell proliferation, migration, malignancy, inflammation, neurodegenerative & cardiac diseases.
- Genetic mutation in RTK → ↑ cell proliferation
- **Inhibitors of RTK:**

  Traztuzumab, cefuximab (mAb inhibits growth factor binding, extracellularly).

  Gefitinib, imatinib, erlotinib (inhibit kinase activity in the cytoplasm).
- Are used for cancer treatment


A
Growth factor
Receptor domain
Transmembrane α helix
Tyrosine kinase domain
Tyrosine residue
Conformation change Dimerisation
Tyrosine autophosphorylation
Phosphorylation of Grb2
Grb2
Binding of SH2-domain protein (Grb2)
Activation of Ras GDP/GTP exchange
MEMBRANE
Ras
GDP
GTP
Activation
Raf
Phosphorylation
Mek
Phosphorylation
Map kinase
Phosphorylation
KINASE CASCADE
Various transcription factors
NUCLEUS
Gene transcription

The activation of Ras by an activated receptor tyrosine kinase



2. **Serine/ threonine kinases:**

   Similar to RTK but phosphorylates serine or threonine residues, e.g. transforming growth factor (TGF-β).

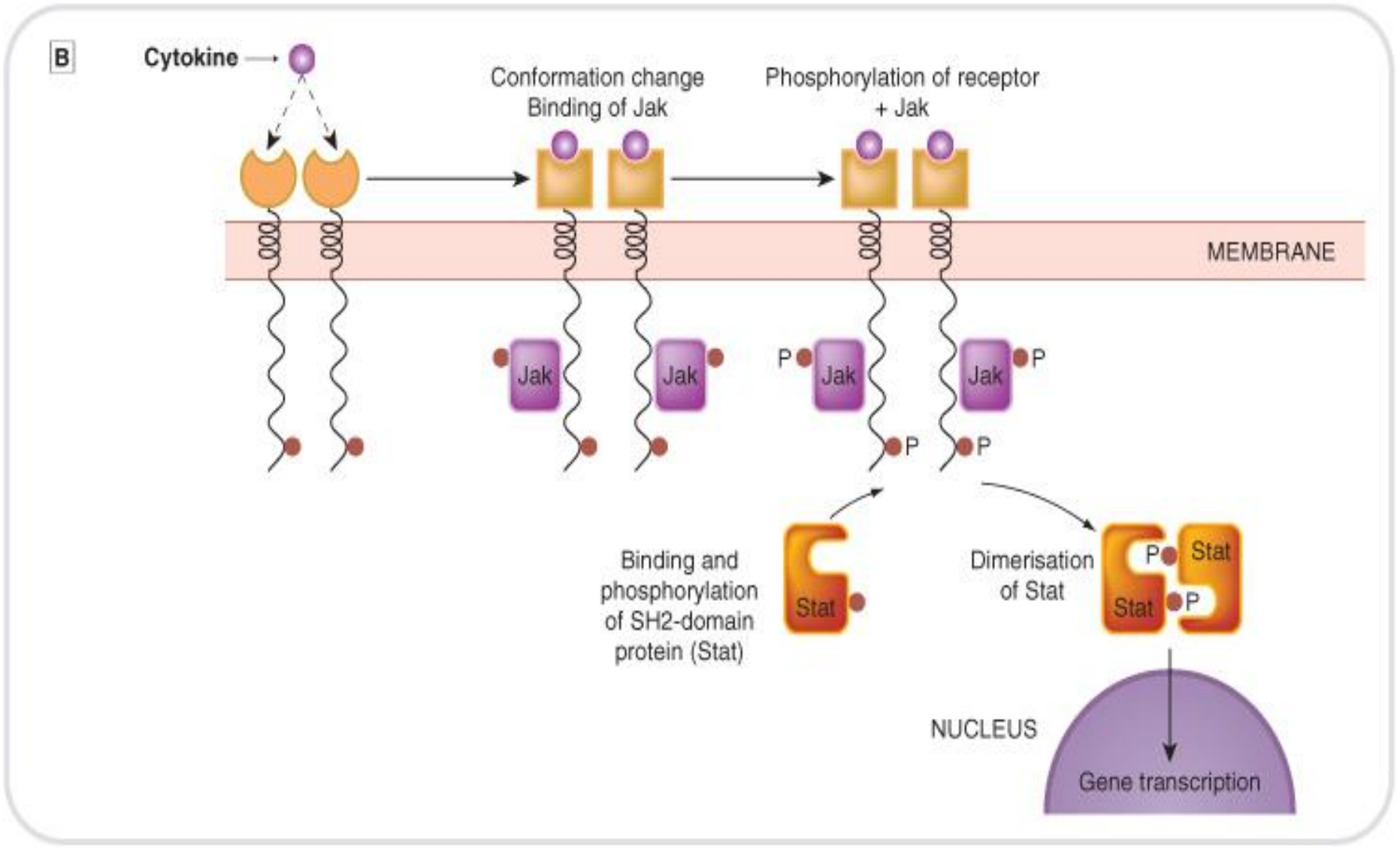
3. **Cytokine receptors:**

   Lack intrinsic enzyme activity. They include cytokines receptors (interferon & colony-stimulating factor receptors…..etc).

Signal transduction mechanism: involves

- Occupation & dimerization of the receptor
- Binding to a cytosolic tyrosine kinase, Jak (Janus Kinase) → trans-phosphorylation of Jak & tyrosine residue → STAT (signal transducer & activator of transcription) phosphorylation & dimerization→ migration to the nucleus→ bind to specific response elements → gene transcription.
- Jak /STAT pathway play a central role in immune responses, cancer, vascular disease & atherosclerosis

Janus kinase (JAK) is a family of intracellular, non-receptor tyrosine kinases that transduce cytokine-mediated signals via the JAK-STAT pathway.

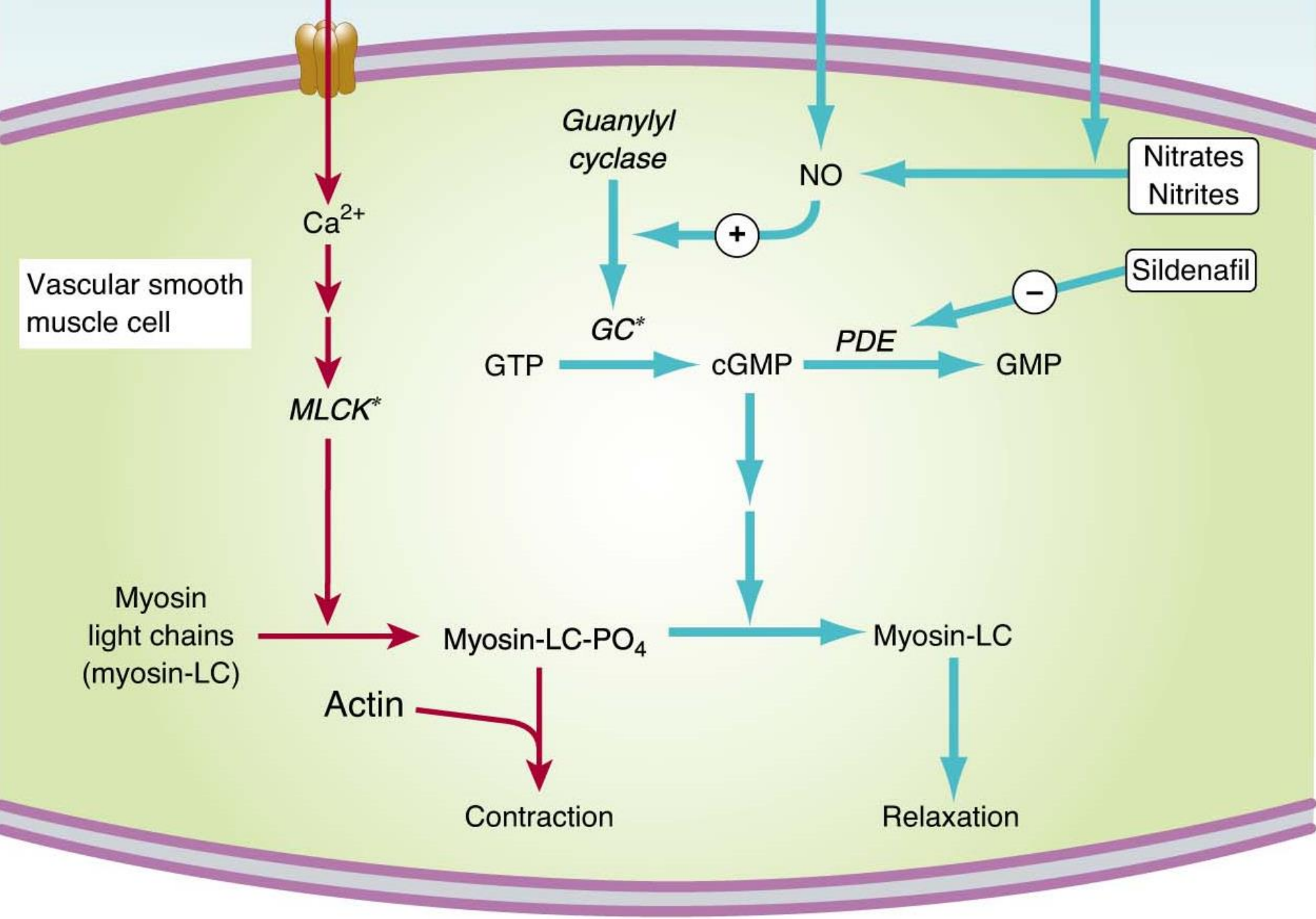


4. **Guanylate cyclase linked receptor:**

Ligands: natriuretic peptides (ANP).

Signal transduction mechanism:

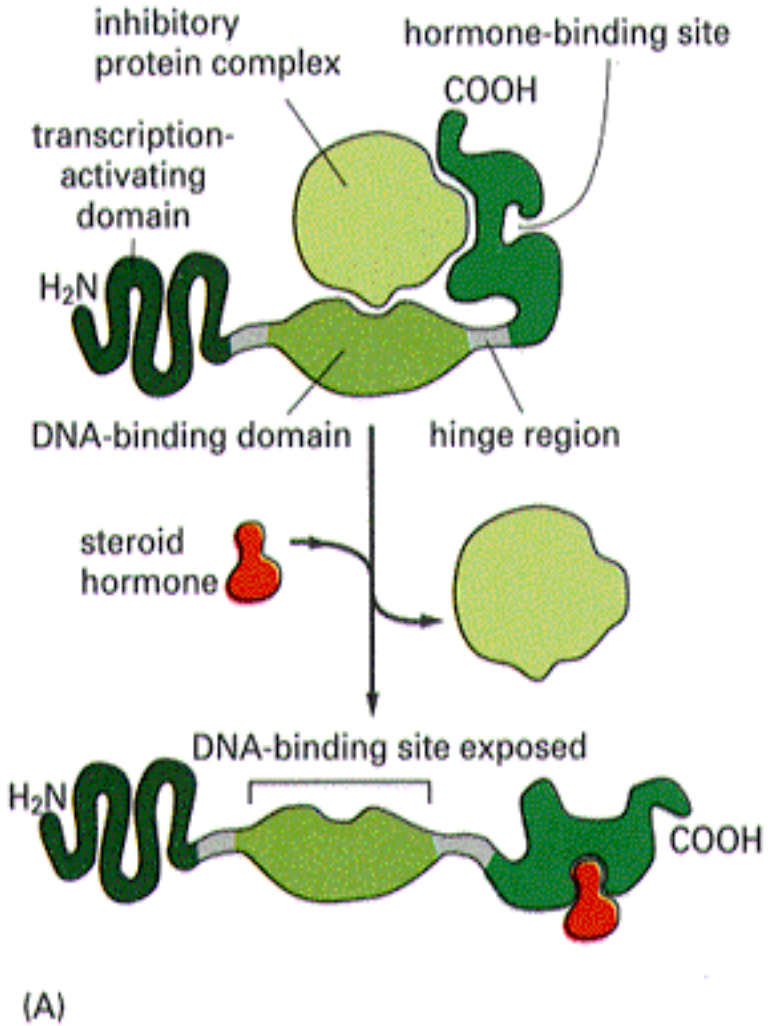
- Dimerization
- Guanylate cyclase stimulation → convert GTP into cGMP → stimulate protein kinase G (PKG) → smooth muscle relaxation (dephosphorylation of myosin light chain).


Guanylyl cyclase
NO
Nitrates
Nitrites
Ca2+
+
Vascular smooth muscle cell
Sildenafil
−
GC*
PDE
GTP
cGMP
GMP
MLCK*
Myosin light chains (myosin-LC)
Myosin-LC-PO4
Myosin-LC
Actin
Contraction
Relaxation

4\ Receptor that regulate gene transcription (Steroid or nuclear receptor):

- Intracellular receptors include steroid, thyroid hormones, Vit D & A receptors, also receptors for certain drugs (glitazones & clofibrate).
- Transduction: hours
- **Structure:**
- A single polypeptide chain with 3 domains:

1. Ligand binding domain (C-terminus)
2. DNA binding domain
3. Transcription activating domain (N-terminus)


inhibitory
protein complex
hormone-binding site
COOH
transcription-
activating
domain
H_2N
DNA-binding domain
hinge region
steroid
hormone
DNA-binding site exposed
H_2N
COOH

(A)

- **Signal transduction mechanism:**
- In the absence of the ligand, the intracellular receptor binds to a heat shock protein (hsp90).
- When the ligand (lipophylic) enters the cell → ligand-receptor complex, triggers the release of hsp90 → dimerization → translocation to the nucleus → binds to hormone response element (RE) → stimulates or inhibits gene transcription.
- Signaling is characterized by:
- Slow onset of action (ligands cannot be used to relief acute attacks (glucocorticoids vs β_2 agonists for acute bronchial asthma).
- Long duration of action (the beneficial or toxic effect decreases slowly after cessation of the drug).

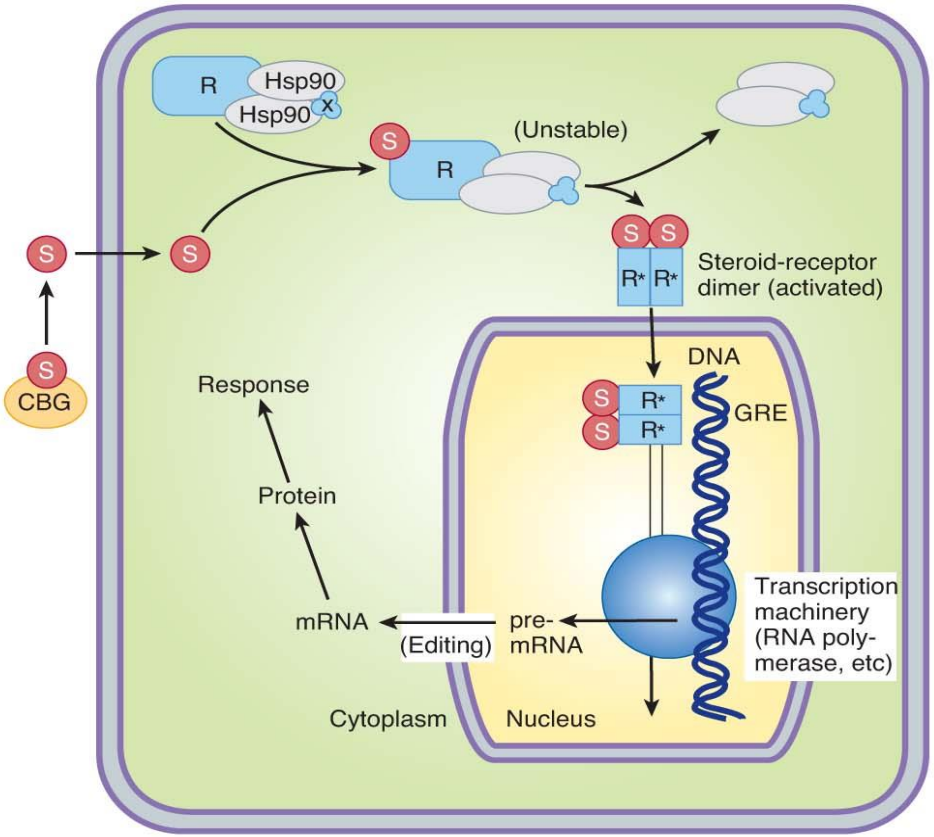


FIGURE 39–4 A model of the interaction of a steroid, S (eg, cortisol), and its receptor, R, and the subsequent events in a target cell. The steroid is present in the blood in bound form on the corticosteroid-binding globulin (CBG) but enters the cell as the free molecule. The intracellular receptor is bound to stabilizing proteins, including two molecules of heat shock protein 90 (Hsp90) and several others, denoted as "X" in the figure. This receptor complex is incapable of activating transcription. When the complex binds a molecule of cortisol, an unstable complex is created and the Hsp90 and associated molecules are released. The steroid-receptor complex is now able to dimerize, enter the nucleus, bind to a glucocorticoid response element (GRE) on the regulatory region of the gene, and regulate transcription by RNA polymerase II and associated transcription factors. A variety of regulatory factors (not shown) may participate in facilitating (coactivators) or inhibiting (corepressors) the steroid response. The resulting mRNA is edited and exported to the cytoplasm for the production of protein that brings about the final hormone response. An alternative to the steroid-receptor complex interaction with a GRE is an interaction with and altering the function of other transcription factors, such as NF-κB in the nucleus of cells.

Receptors and diseases

- Receptor's diseases can be produced by two major mechanisms:

1. **Auto-antibodies directed against receptor's protein.**

- Auto-antibodies inactivate nAch receptor e.g. Myasthenia gravis.
- Anti-bodies can also mimic the effects of agonists:

  Anti-bodies activating α-receptors (sever hypertension), β-receptors (cardiomyopathy), thyrotropin receptors (thyroid hypersecretion) & glutamate receptors (neurodegenerative disorders).

2. **Mutation in genes encoding receptor, effectors, or coupling proteins.**

- e.g. mutated vasopressin (ADH) and corticotropin (ACTH) receptors are resistant to the actions of these hormones.
- Mutation of the receptor may results in activation of effector mechanisms in the absence of the agonist.
- e.g. Mutation of the genes encoding growth factor receptor, kinases (malignancy).

Variation in Drug Responsiveness

- Quantitative or qualitative variation:

A. Quantitative variation in drug response:

- **Tolerance:**

  Gradual decrease in drug response as a result of continuous or repeated drug administration. It takes days or weeks e.g. barbiturates, nitrates

- **Tachyphylaxis or desensitization:**

  The response of the drug is diminished rapidly (min.-hr) after repeated administration of the drug. e.g. amphetamine

- **Drug resistance:** loss of effectiveness of antimicrobial or antitumor drugs.

B. Qualitative variation in drug response:

- **Idiosyncratic drug response:**
- It is genetically determined abnormal & harmful drug response occurs, rarely and unrelated to the dose of the drug (may be due to immunological reactions or genetic abnormality)
- Examples:
- Penicillins → HSR

- **Genetic polymorphism**
- oxidation rate (↓ oxidation rate →TCA toxicity)
- acetylation rate (↓acetylation rate (slow acetylators)→ INH peripheral neuropathy).

  (↑acetylation rate (fast acetylators → INH hepatotoxicity).
- Suxamethonium → suxamethonium apnea due to the presence of abnormal type of cholinesterase that fails to inactivate suxamethonium rapidly leading to prolongation of suxamethonium duration of action.
- Primaquine, sulfonamides & dapsone cause hemolytic anemia in individuals with G-6-PD deficiency.
- Chloramphenicol → aplastic anemia.

- ***The mechanisms for variation in drug response:***

1. **Alteration in the numbers of receptors**:

- Down regulation: is gradual decrease in the numbers of the receptors (internalization) due to prolong exposure of the receptor to an agonist. e.g. β-agonists
- Up-regulation: ↑ numbers of the receptors e.g. →up regulation of β receptors in the heart by chronic administration of receptor blocker.

2. **Change in receptors:**

Conformational change in the ion channel linked receptor (nAch) → desensitization

Phosphorylation of G-protein coupled receptor → desensitization

3. **Exhaustion of mediators:**

Amphetamine desensitization occurs due to depletion of the stored noradrenaline

4. **Increased metabolic degradation:**

Tolerance to some drugs (barbiturates & phenytoin) occurs due to auto-induction (↑ their own metabolism).

5. **Physiological adaptation:**

- The development of homeostatic response decreases drug response. Antihypertensive effect of thiazide diuretic is limited due to activation of renin-angiotensin system. Physiological adaptation decreases many side effects during drug administration.

6. **Active extrusion of the drug from the bacterial or parasitic cell:**

Results in resistance to antimicrobial agents e.g. tetracycline resistance