

Receptors

B.Sc. Pharmacology & Translational Medical Science, yr 2

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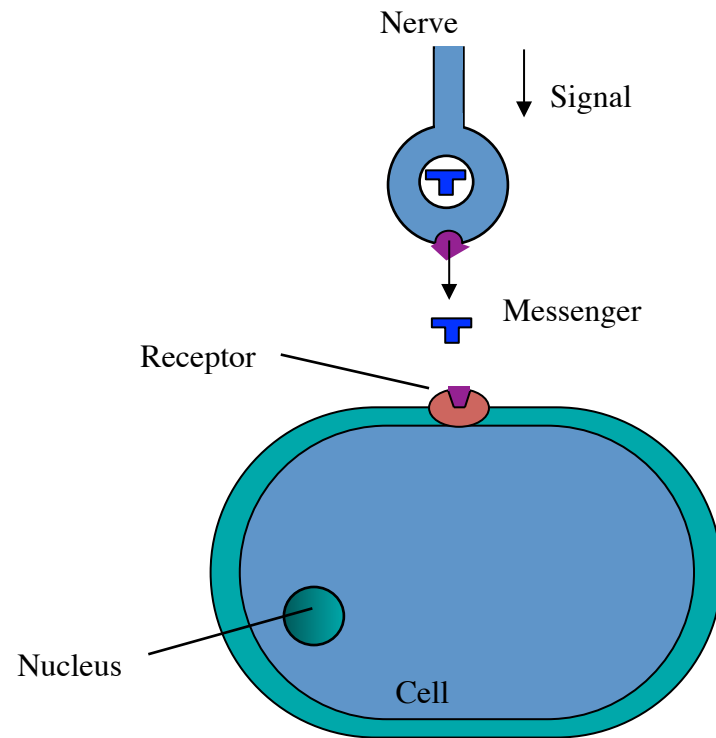
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Learning objectives

- The role of receptors and why they are good drug targets
- Types of receptors
 - Ligand-gated ion channels
 - G-protein coupled receptors
 - Kinase-linked receptors
 - Nuclear receptors
- How drugs interact with receptors
 - agonism, antagonism

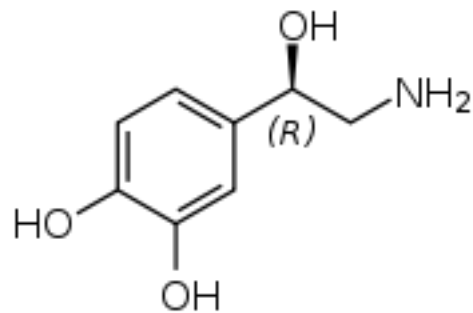
What are receptors? How do they work?



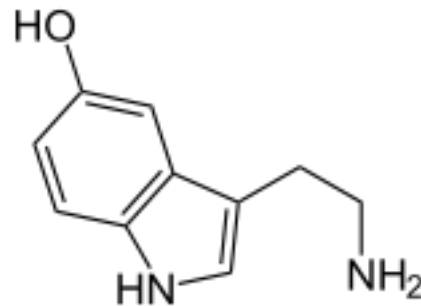
- Communication between nerves and cells
- Nerves in CNS send messages to target cells
- Cells of one tissue send messages to other cells
- Chemical messenger = neurotransmitter or hormone

Typical neurotransmitters

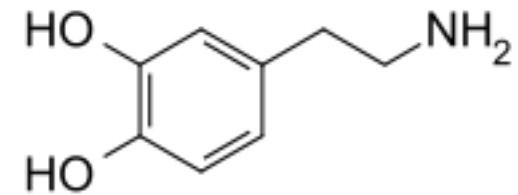
- Cover gap between nerve and cell
- Structures vary
 - Ions
 - Lipids, purines, peptides
 - Monoamines, amino acids



Noradrenaline



Serotonin

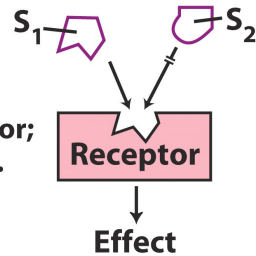


Dopamine

Hormones

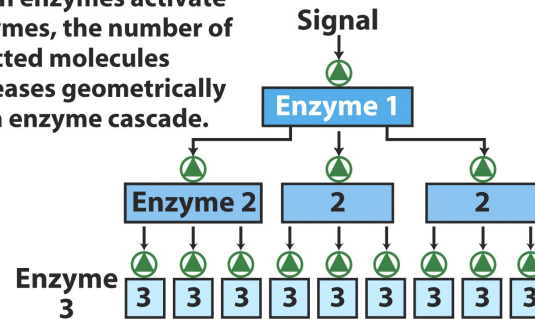
(a) Specificity

Signal molecule fits binding site on its complementary receptor; other signals do not fit.



(b) Amplification

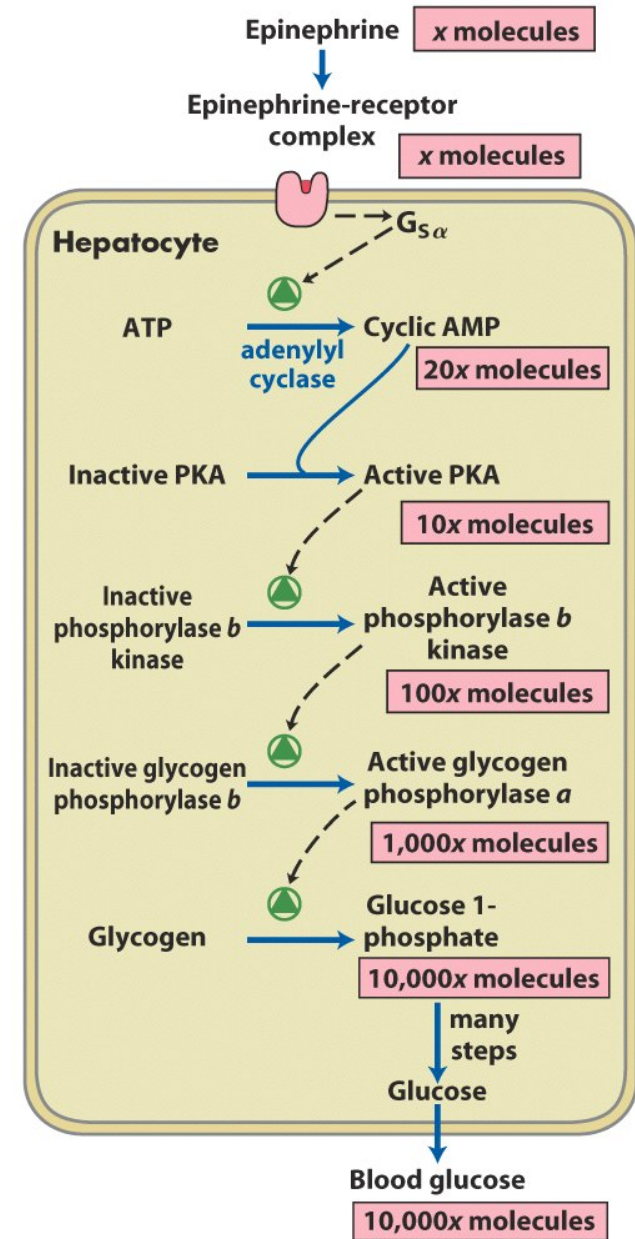
When enzymes activate enzymes, the number of affected molecules increases geometrically in an enzyme cascade.



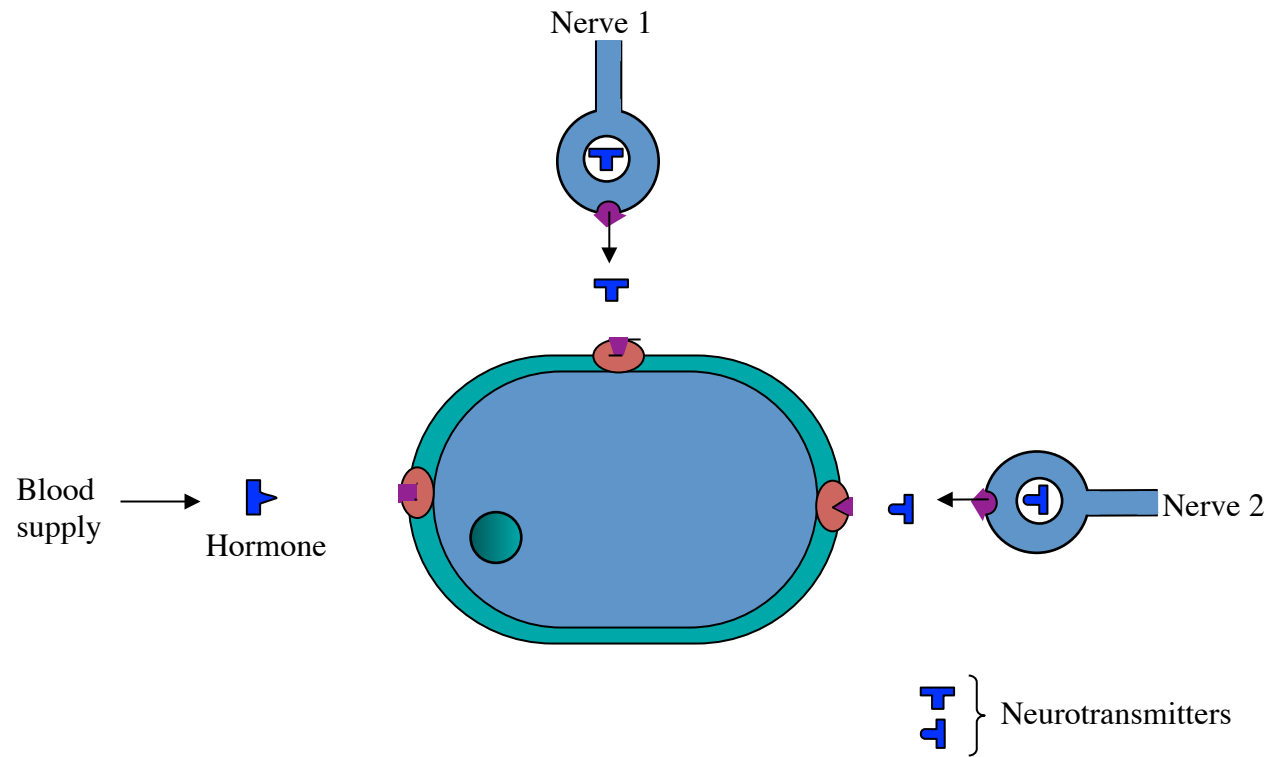
■ Endocrine, paracrine, autocrine

TABLE 23-1 Classes of Hormones

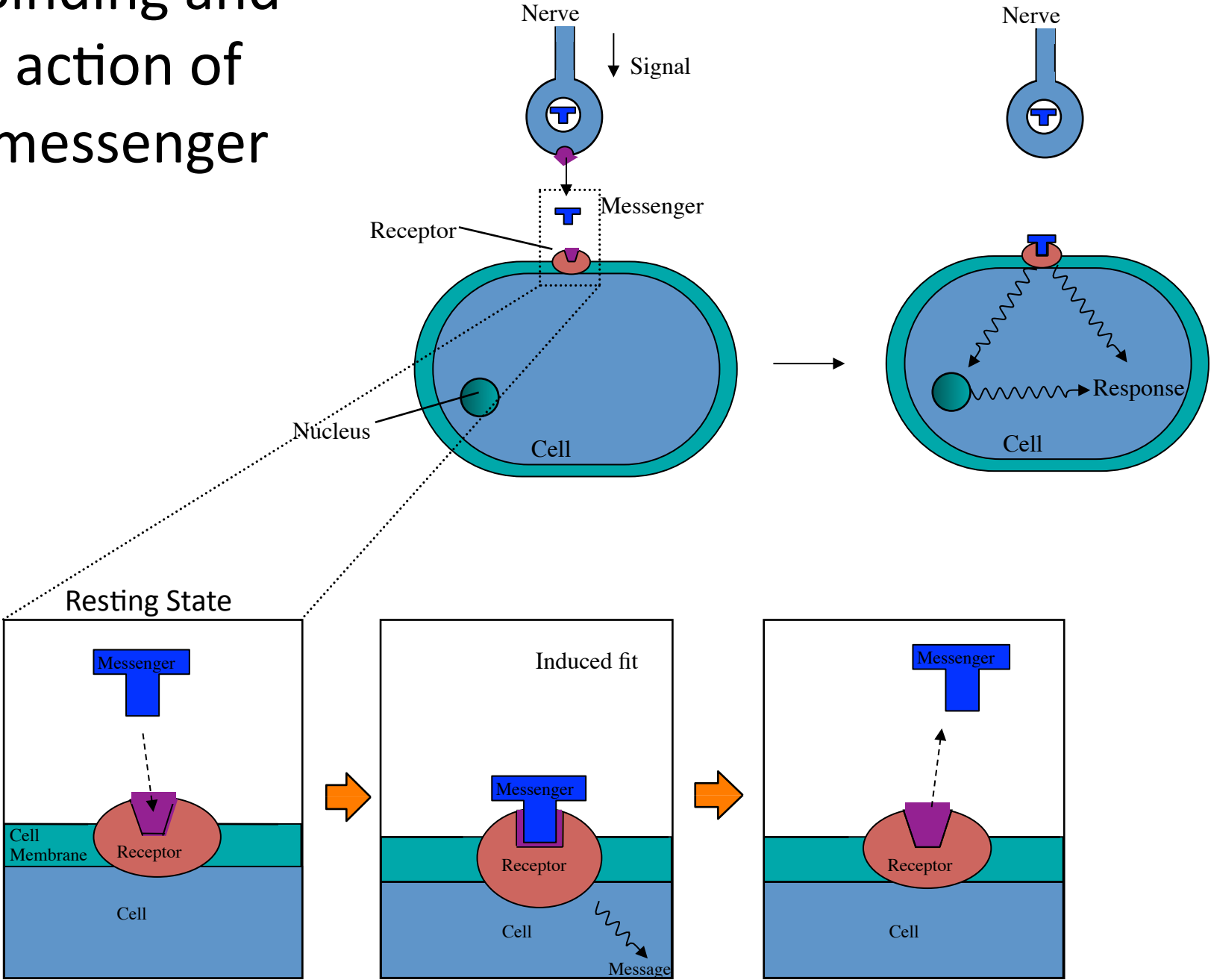
Type	Example	Synthetic path	Mode of action
Peptide	Insulin, glucagon	Proteolytic processing of prohormone	Plasma membrane receptors; second messengers
Catecholamine	Epinephrine	From tyrosine	
Eicosanoid	PGE ₁	From arachidonate (20:4 fatty acid)	Nuclear receptors; transcriptional regulation
Steroid	Testosterone	From cholesterol	
Vitamin D	1,25-Dihydroxycholecalciferol	From cholesterol	Cytosolic receptor (guanylate cyclase) and second messenger (cGMP)
Retinoid	Retinoic acid	From vitamin A	
Thyroid	Triiodothyronine (T ₃)	From Tyr in thyroglobulin	
Nitric oxide	Nitric oxide	From arginine + O ₂	



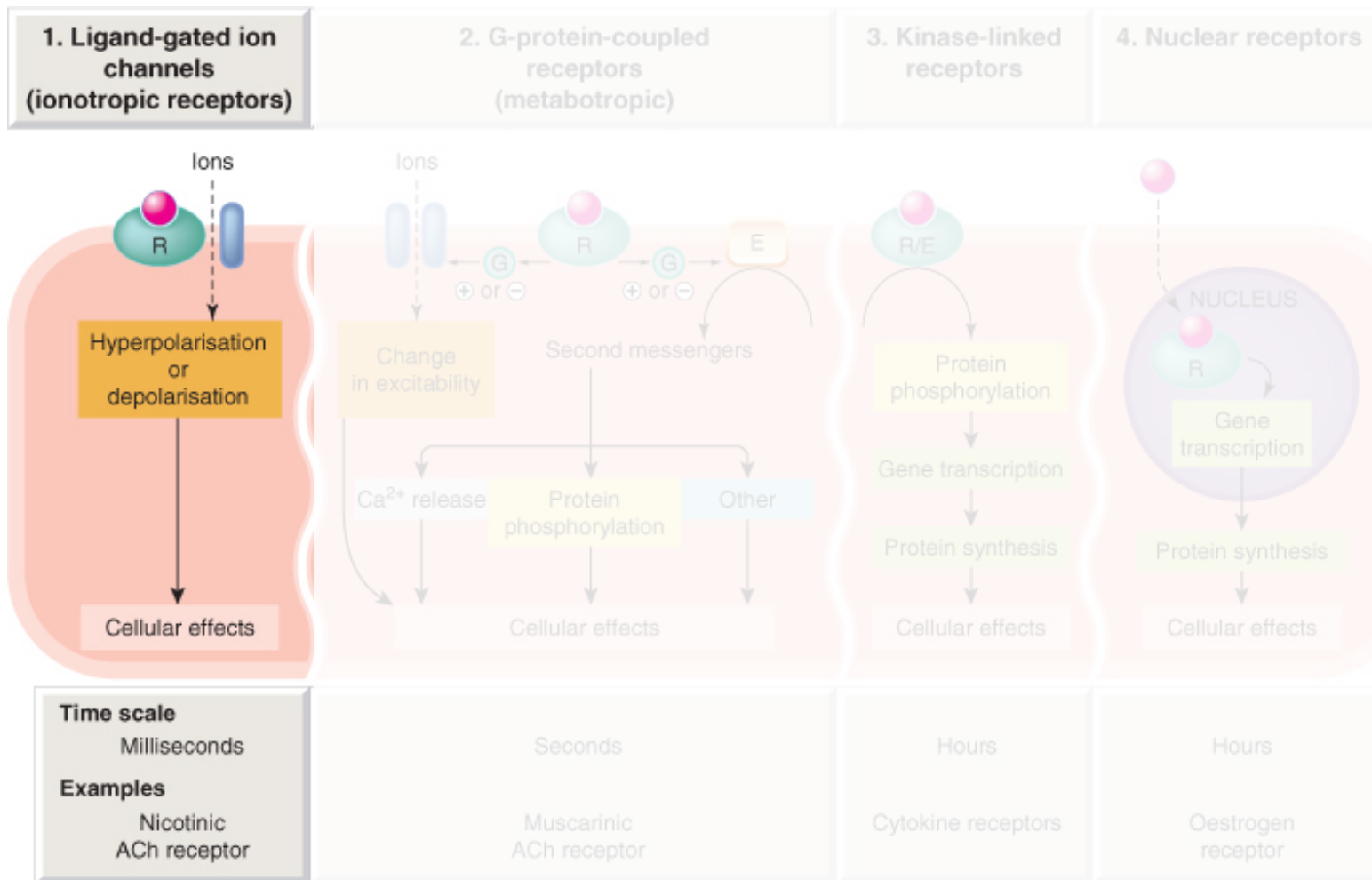
Receptors



Binding and action of messenger

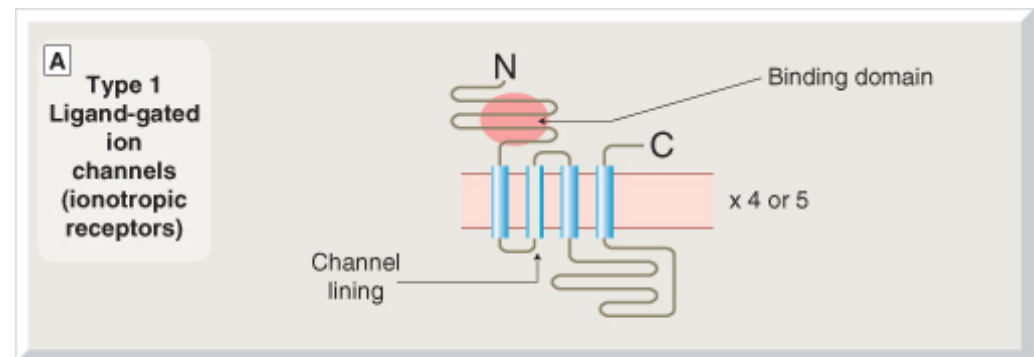


Type 1: ligand-gated ion channels

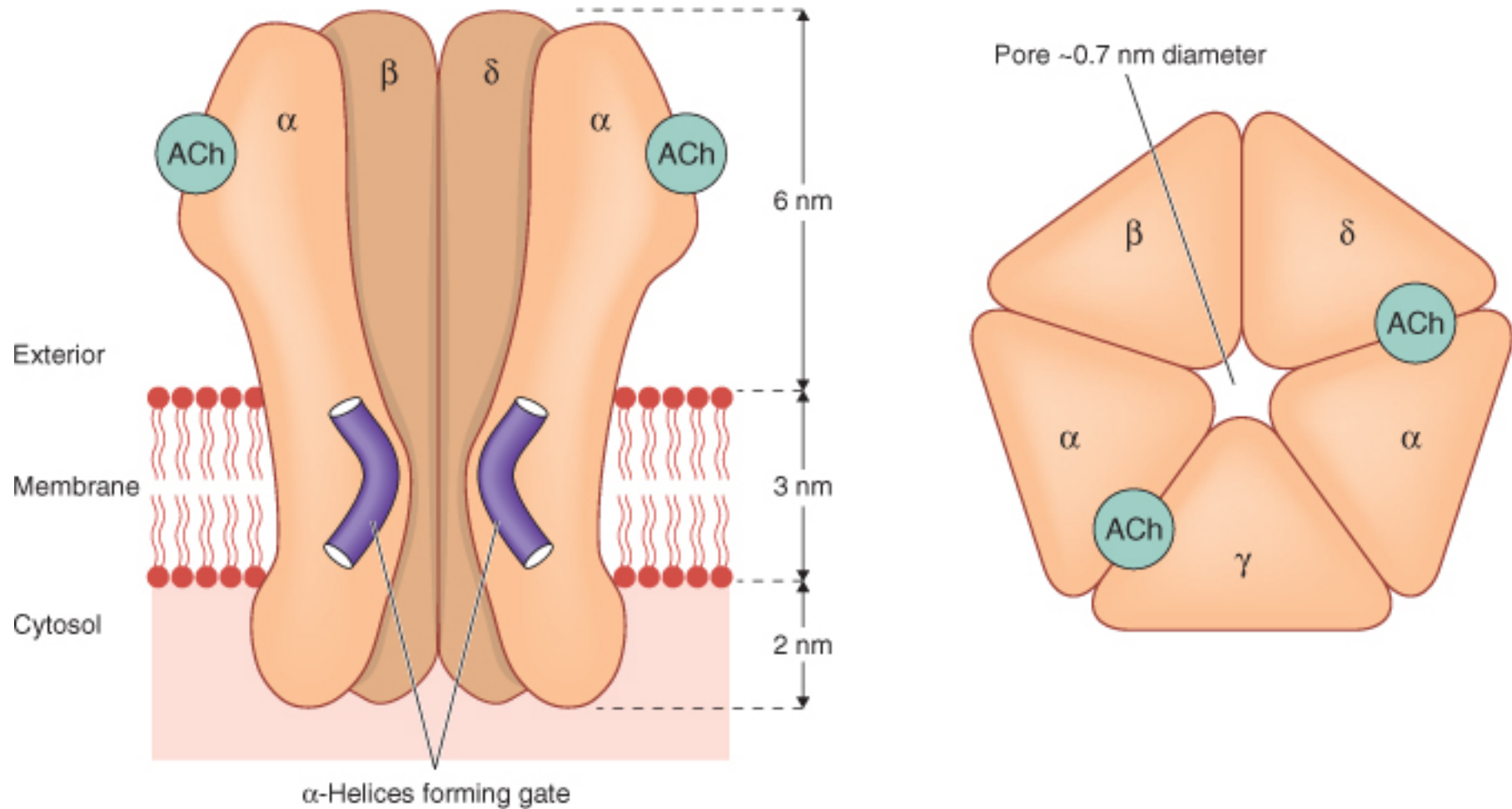


Ligand-gated ion channels

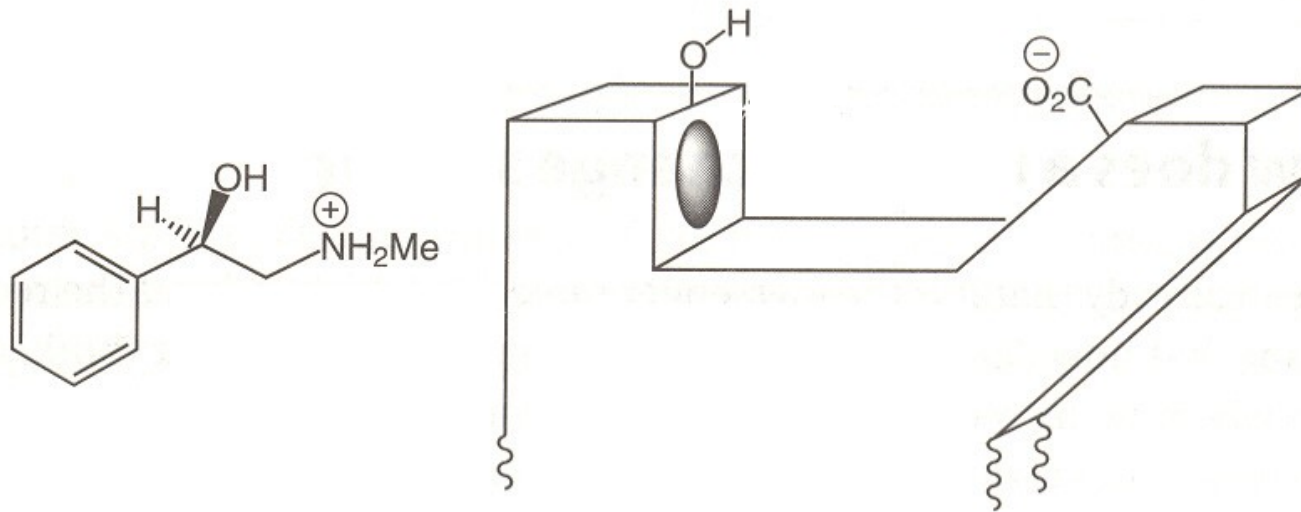
- Ligand-gated ion channels = “ionotropic receptors”
- Respond within milliseconds
- Membrane proteins :
 - made of several subunits
 - structure similar to other ion channels
 - incorporating ligand-binding site = receptor
- Examples:
 - nicotinic acetylcholine receptor
 - GABA_A receptor
 - glutamate receptor



Typical ion channel: Acetylcholine nicotinic receptor

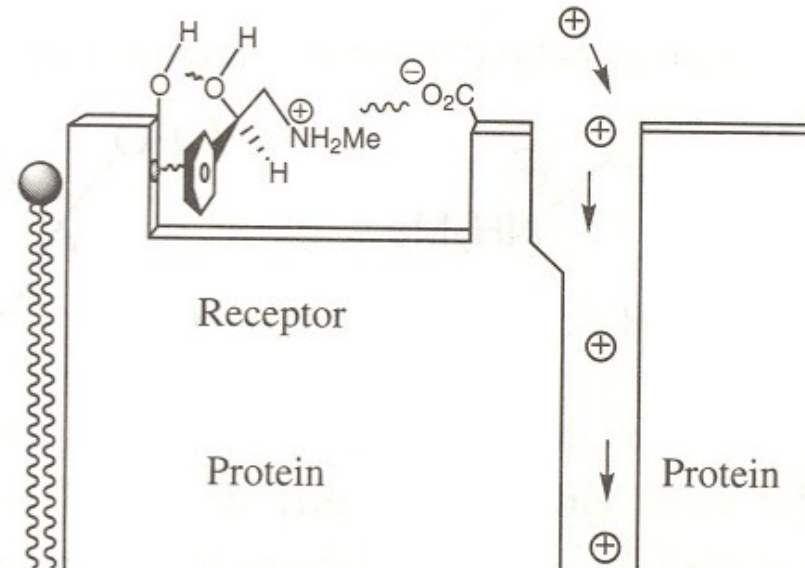
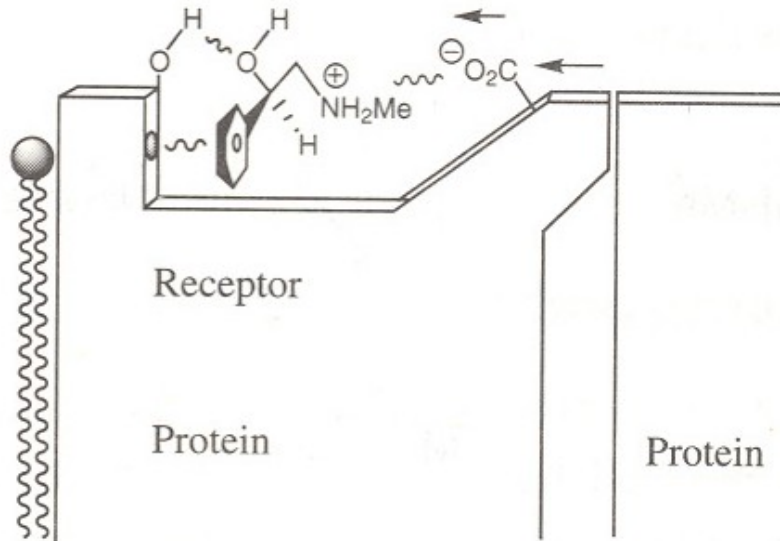
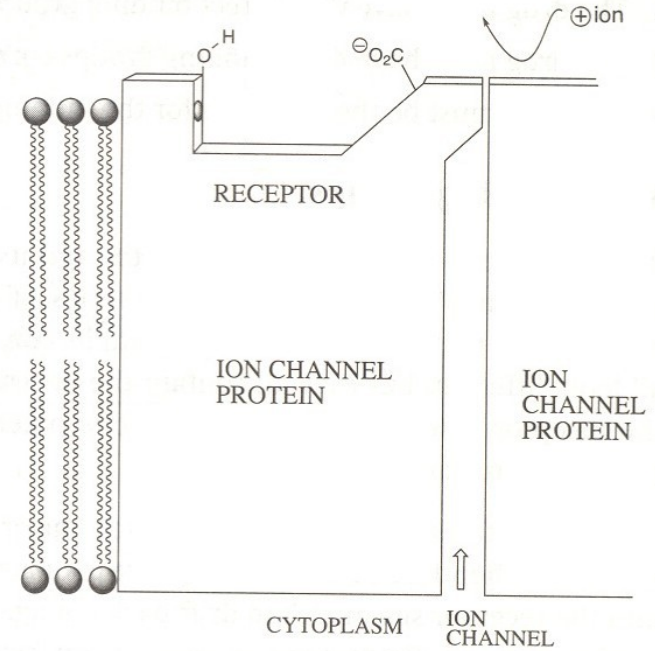
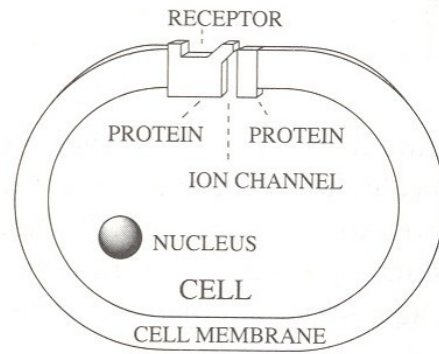


A hypothetical neurotransmitter and receptor:

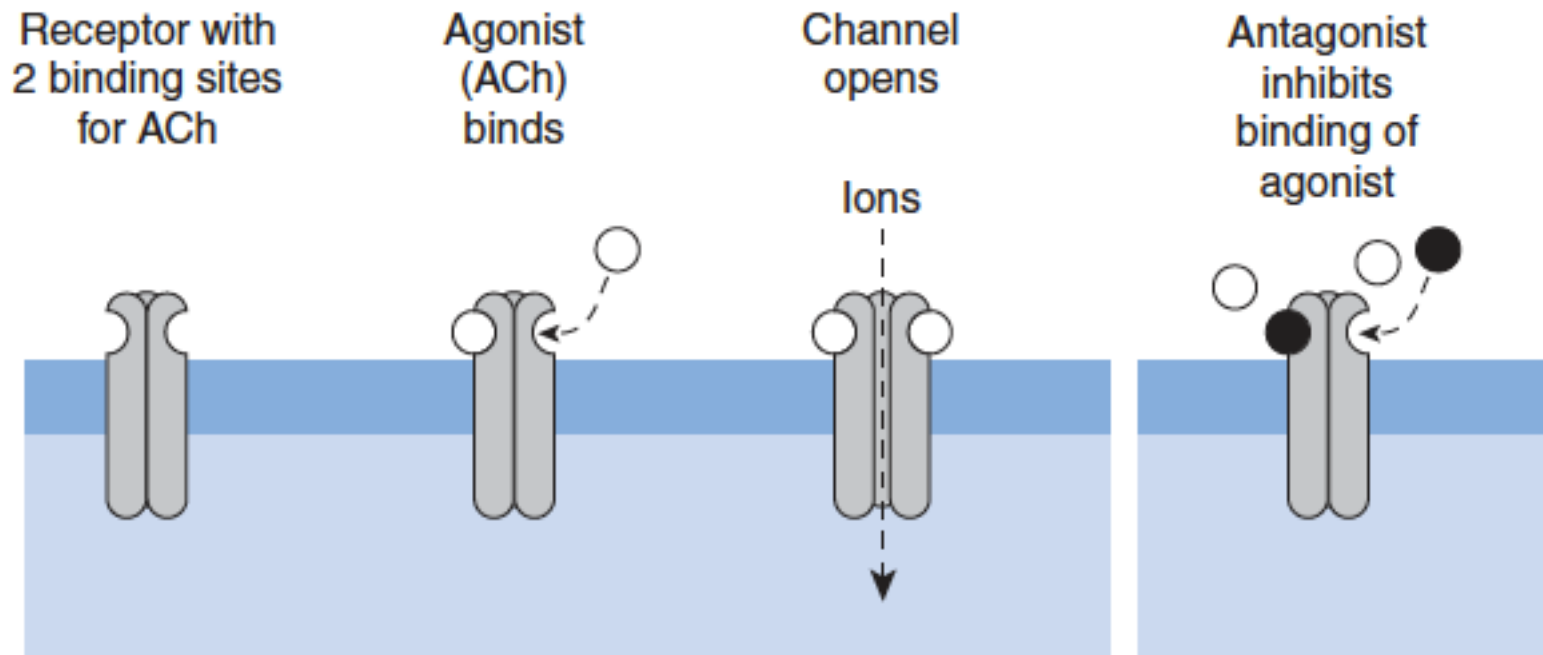


- What binding groups exist on the neurotransmitter?
- On the binding site?

Lock-gate mechanism

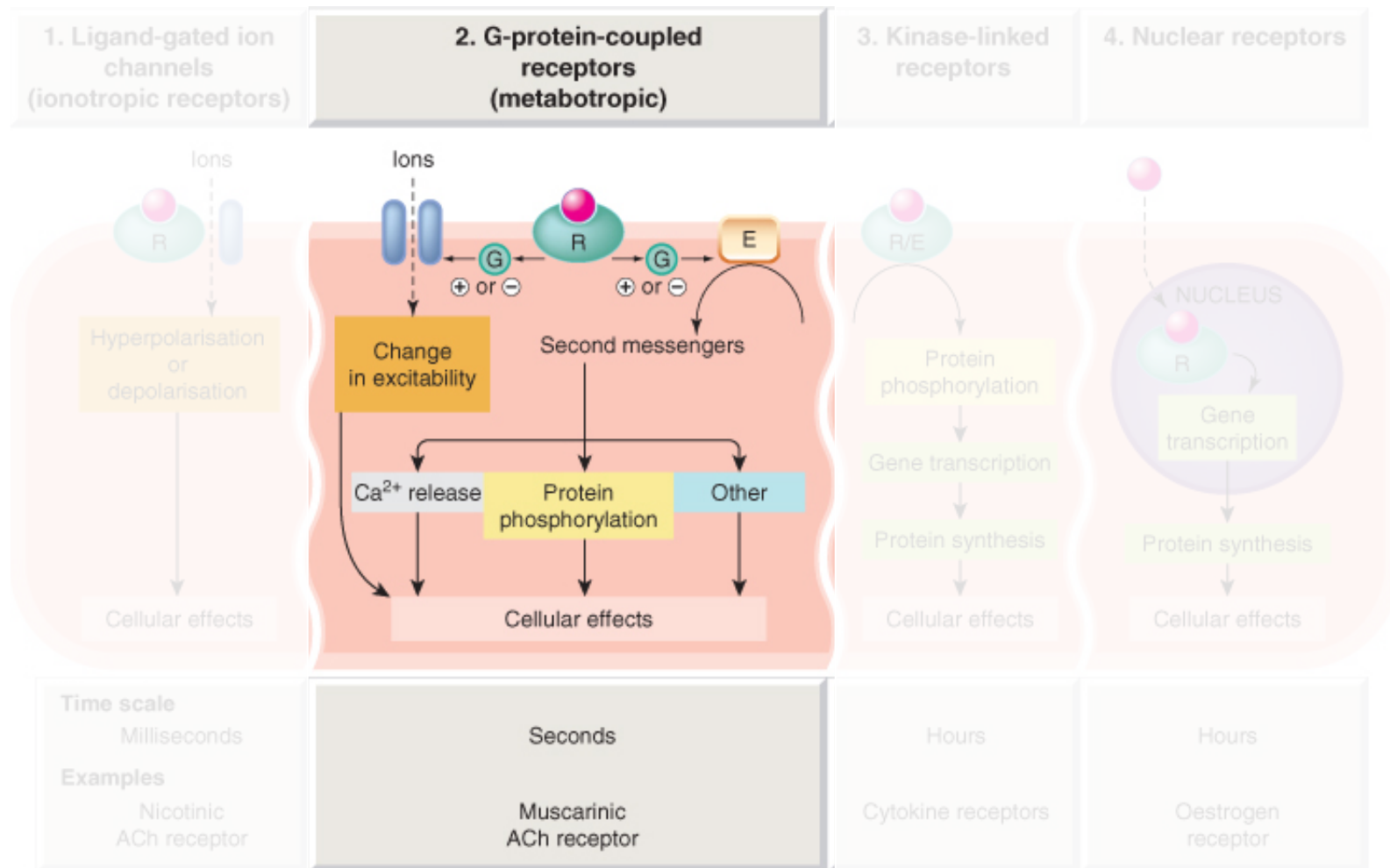


Ach nicotinic receptor



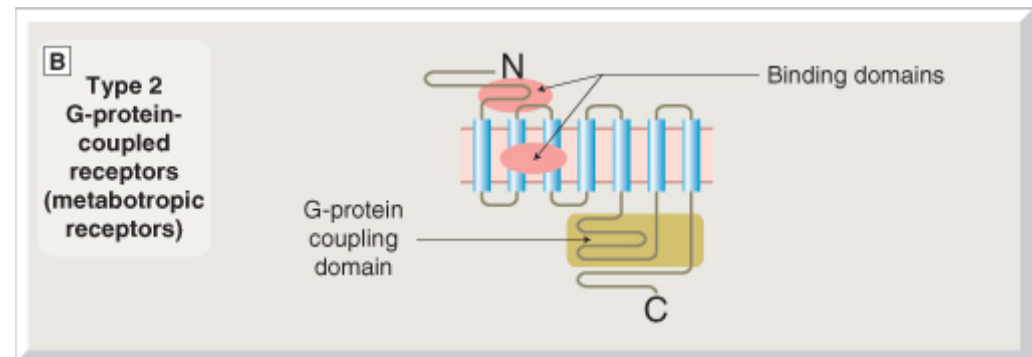
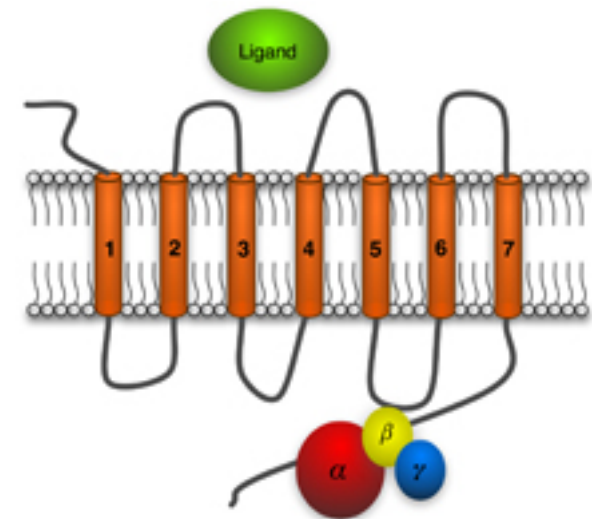
Type 2: G-protein coupled-receptors

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G-protein-coupled receptors

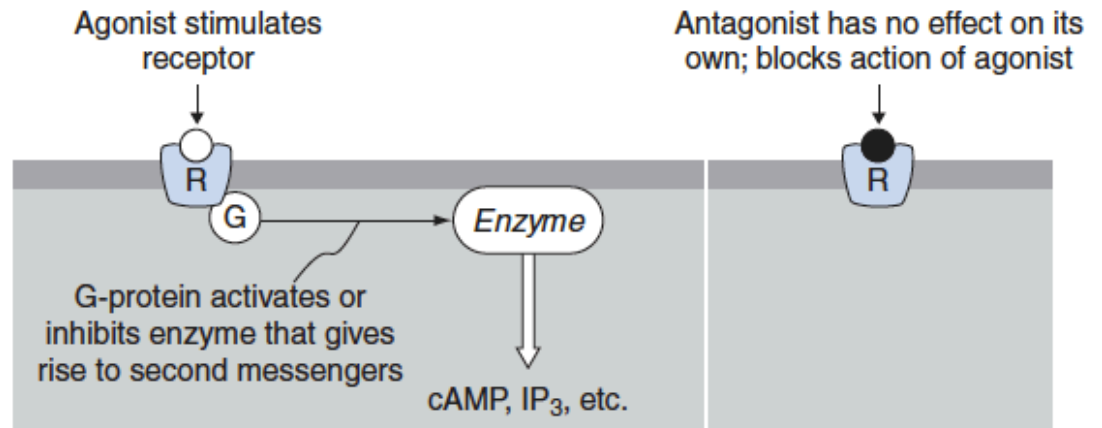
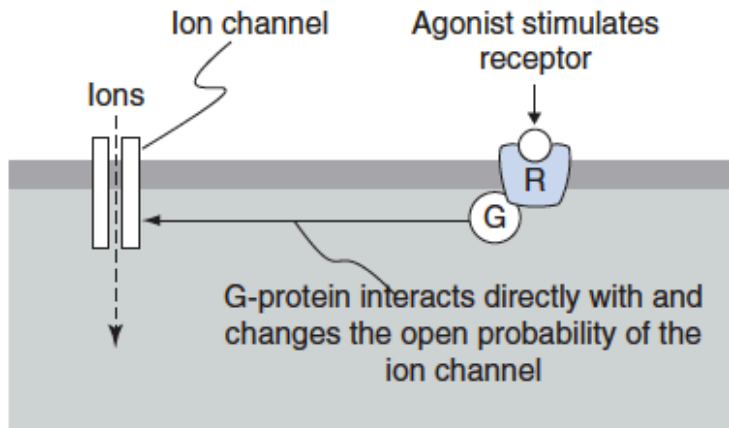
- Receptors coupled to intracellular enzymatic effector systems = “metabotropic receptors”
- Respond within seconds
- transmembrane proteins :
 - Monomeric, but 7 transmembrane domains = “serpentine”, snake-like
 - Coupled to G proteins (guanine nucleotide-binding proteins)
- Examples:
- Muscarinic acetylcholine receptor
- Adrenoreceptors



G-proteins

- Guanine nucleotide-binding proteins
- Heterotrimeric complexes
 - α , β , γ subunits
- $G\alpha$ subunit act as molecular switch
 - guanosine triphosphate (GTP) = activated
 - guanosine diphosphate (GDP) = deactivated
- Different types of subunits => different targets
 - “Second messengers”
- Also small GTPases (not covered)

G-protein-coupled receptors

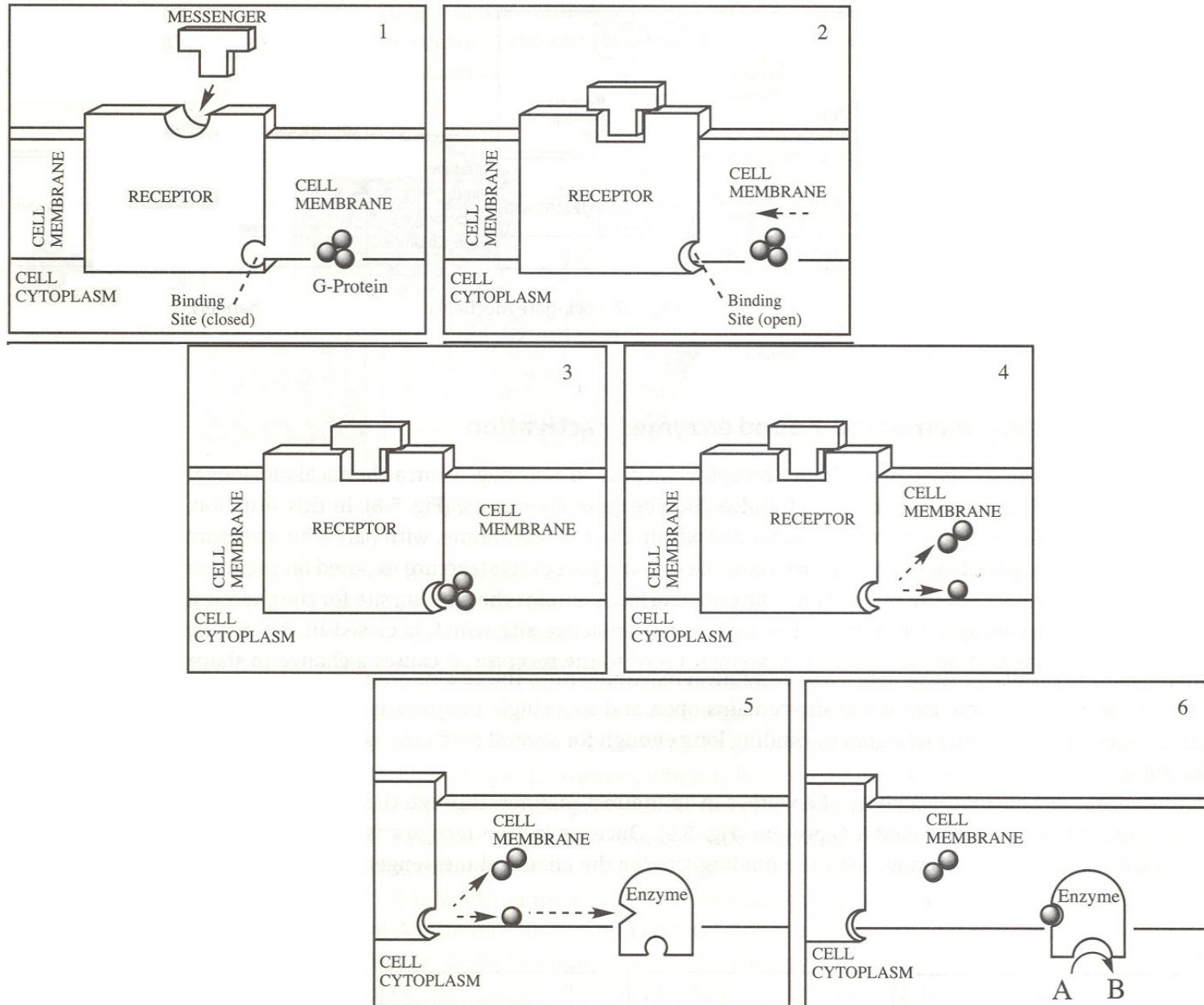


Examples

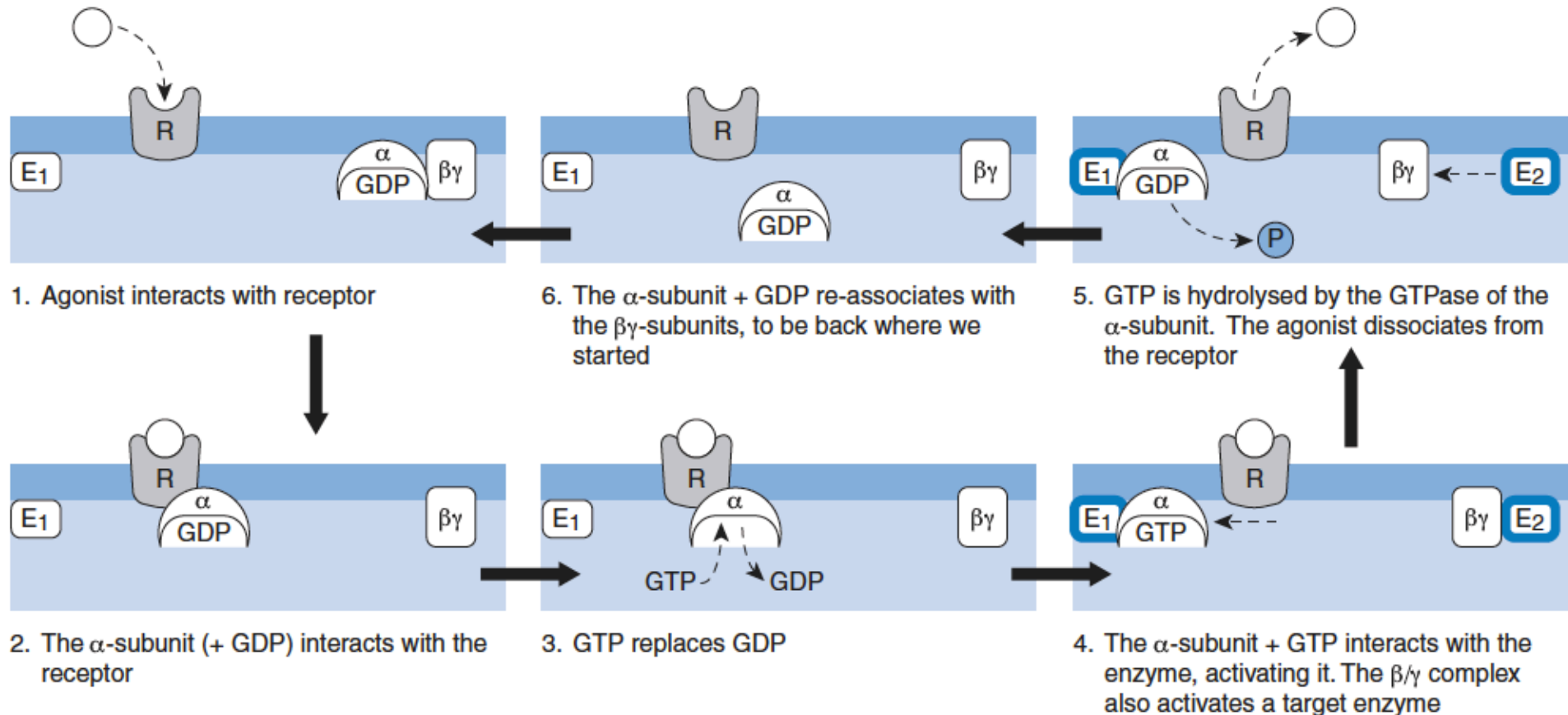
- Muscarinic receptors in heart ↑ K⁺ permeability and ↓ electrical activity
Antagonist: atropine
- Opiates open K⁺ channels and ↓ excitability in neurons
Antagonist: naloxone

	Agonists	Antagonists
β ₂ -Adrenoceptors	Salbutamol	Propranolol
β ₁ -Adrenoceptors	Isoprenaline	Atenolol
H ₁ receptors	Histamine	Mepyramine
H ₂ receptors	Histamine	Ranitidine
Opiate μ receptors	Morphine	Naloxone


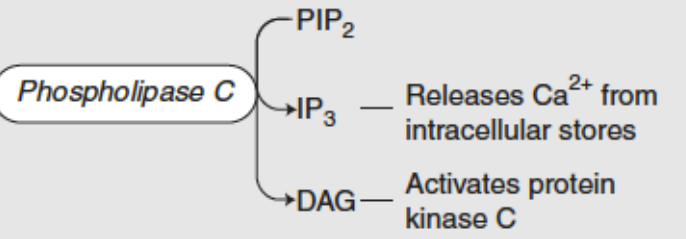

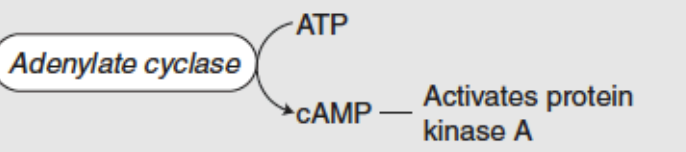
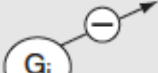

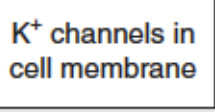
Membrane-bound enzyme activation via G-proteins



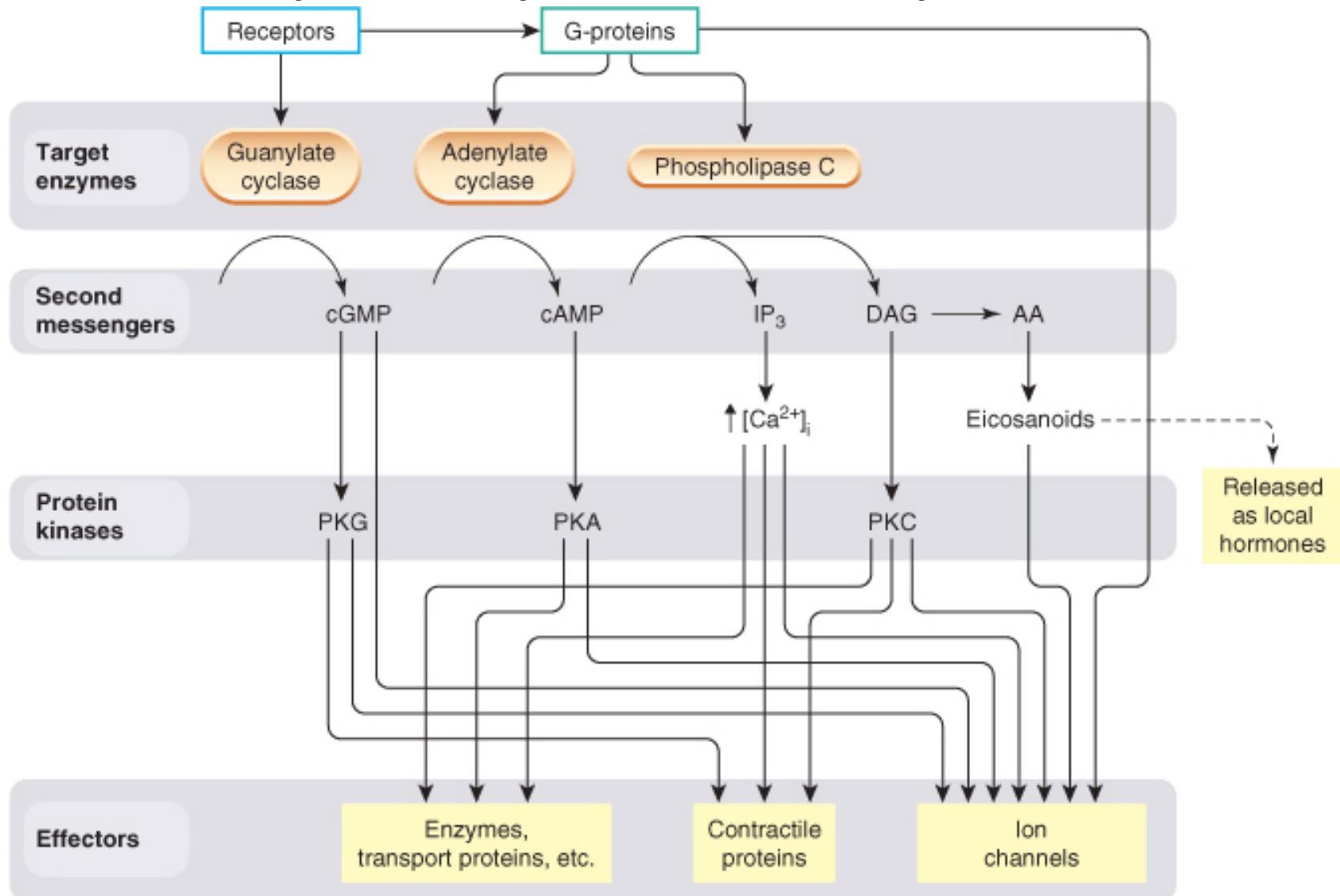
Mechanism of G-protein coupled receptor transduction



Examples of G-protein-coupled actions

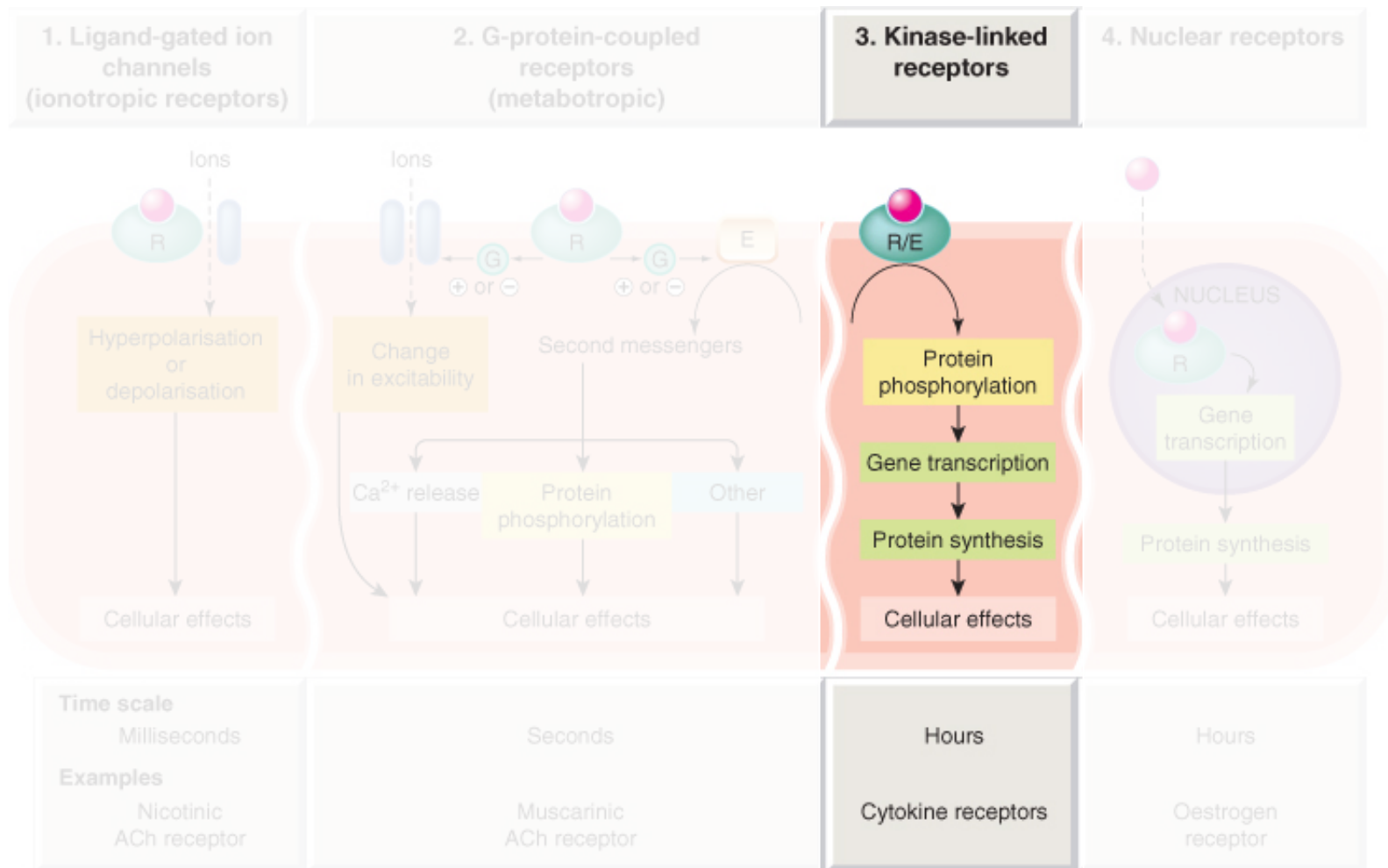
G-proteins	Targets activated	Example of receptor involved	Typical effect	Produced by agonists	Antagonist
		H ₁ -histamine	Smooth muscle contraction (↑IP ₃) A variety of effects due to protein phosphorylation	Histamine Ch. 15	Mepyramine
		β ₂ -Adrenoceptor →	Smooth muscle relaxation (↑cAMP)	Adrenaline Ch. 11, salbutamol Ch. 24	Propranolol
		M ₂ -muscarinic →	Decreased force of contraction of the heart (↓cAMP)	Acetylcholine	Atropine
		M ₂ -muscarinic →	Cardiac slowing	Acetylcholine Ch. 10	Atropine

Diversity of G-protein coupled actions



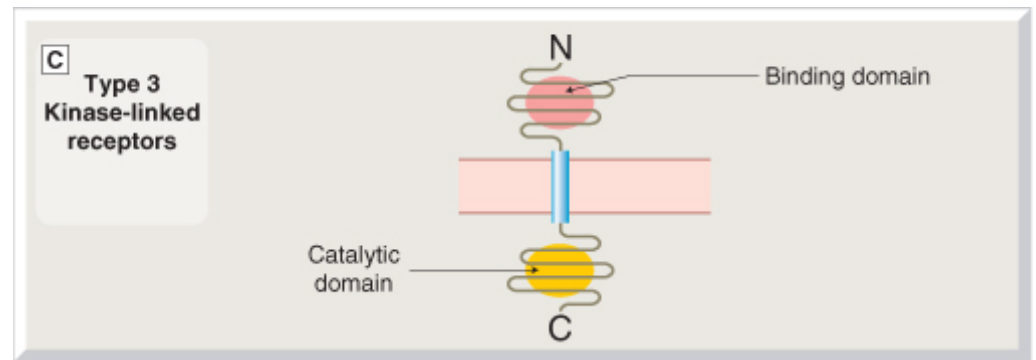
Type 3: Kinase-linked receptors

Type 3: Kinase-linked receptors



Kinase-linked receptors

- Receptors coupled to intracellular kinase
- Respond within hours
- Heterogeneous family of proteins :
 - Monomeric
 - Single transmembrane helix linking extracellular receptor domain to intracellular kinase domain
- Examples:
 - Insulin receptor
 - Growth factor receptor
 - Cytokine receptors
 - etc...



Different types of Receptor Tyrosine Kinases (RTKs)

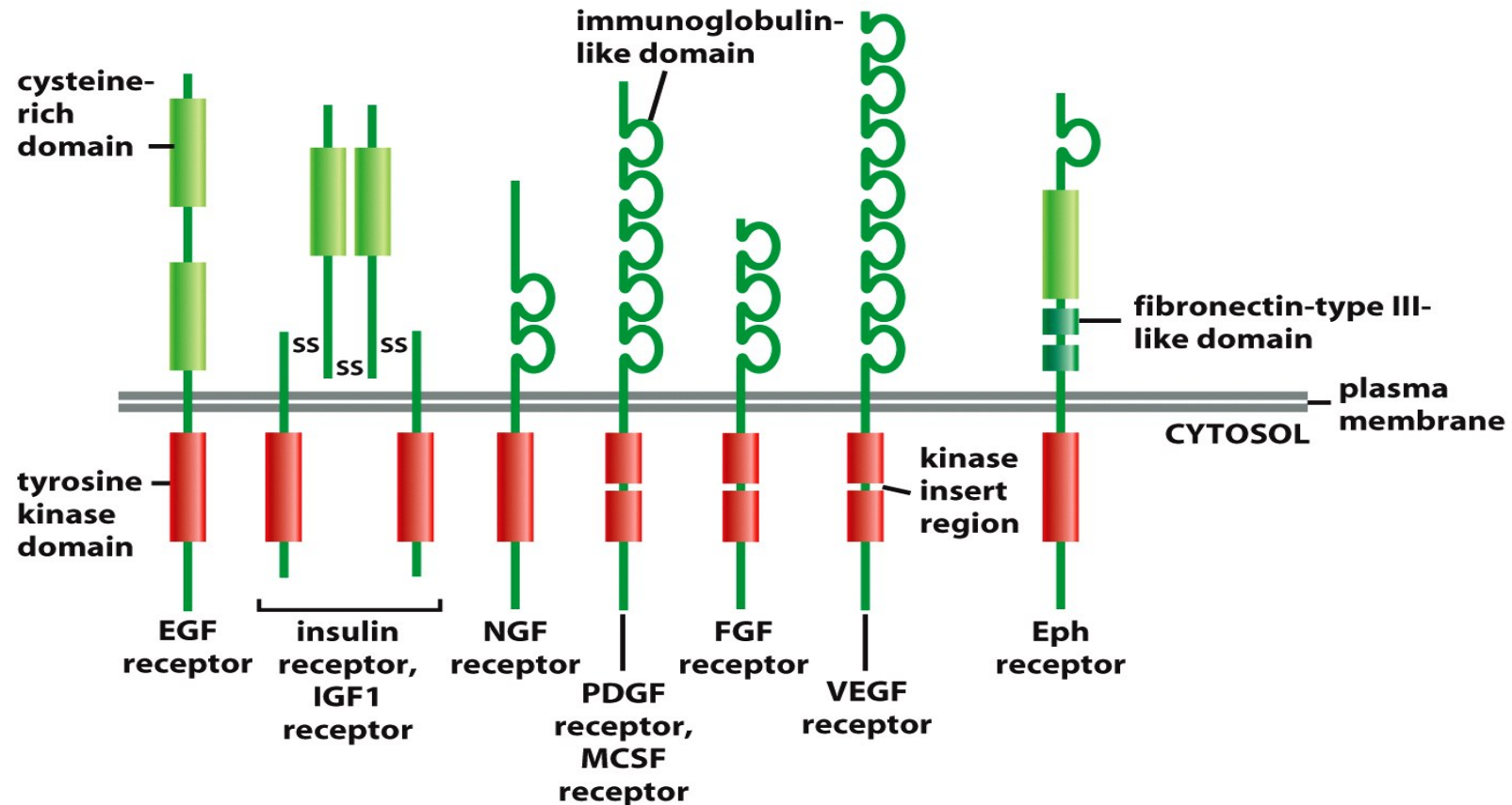


Figure 15-52 Molecular Biology of the Cell 5/e (© Garland Science 2008)

Mechanism of action

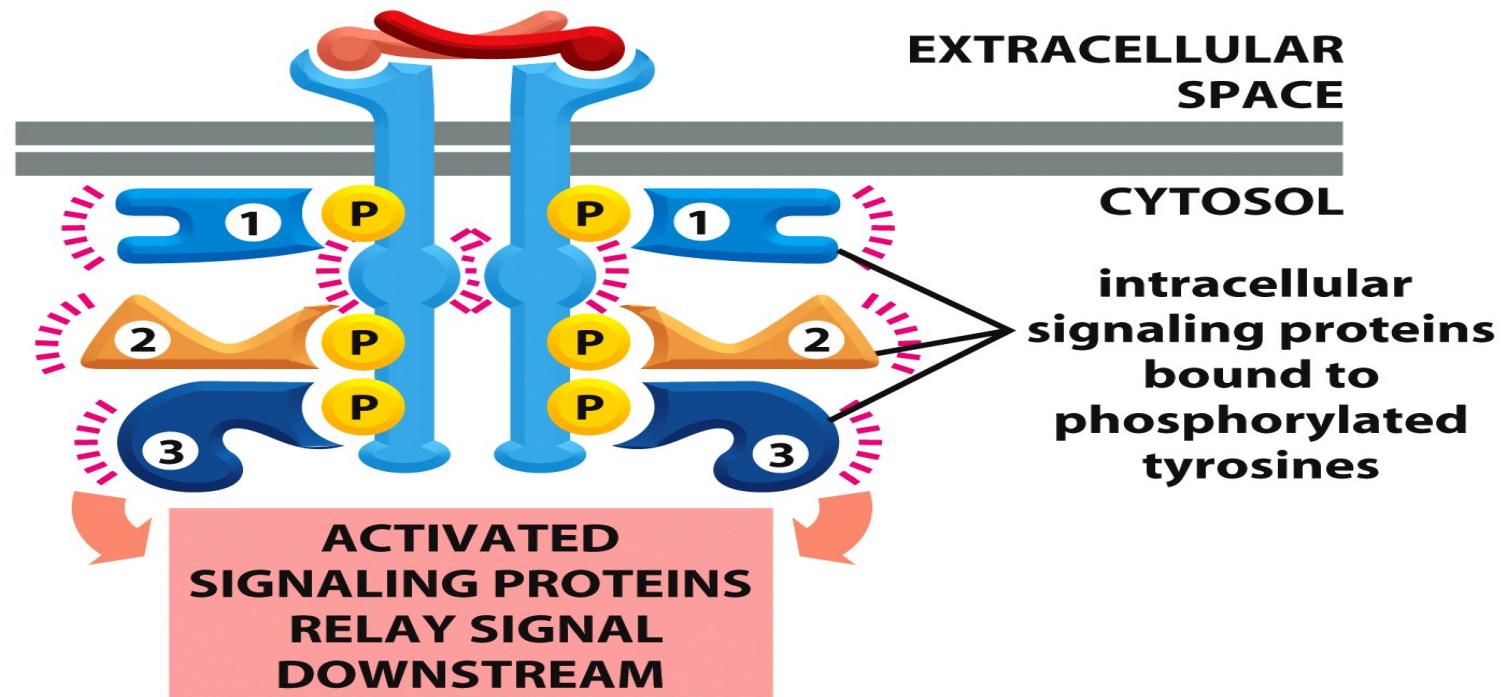
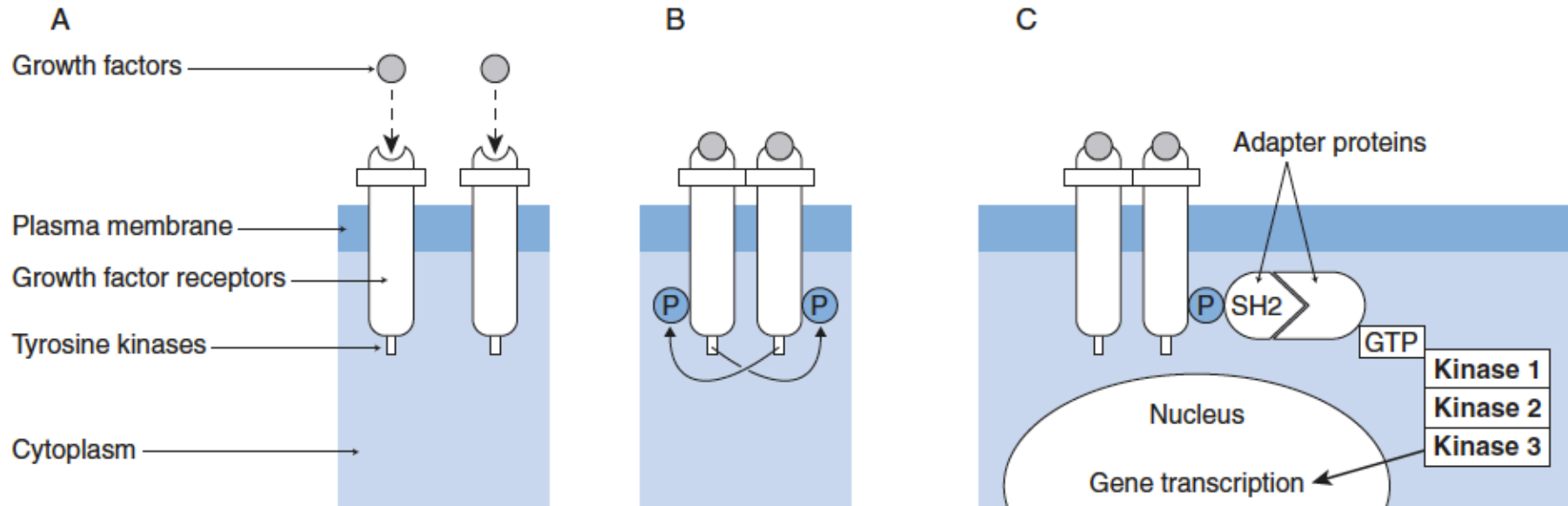


Figure 15-54 Molecular Biology of the Cell 5/e (© Garland Science 2008)

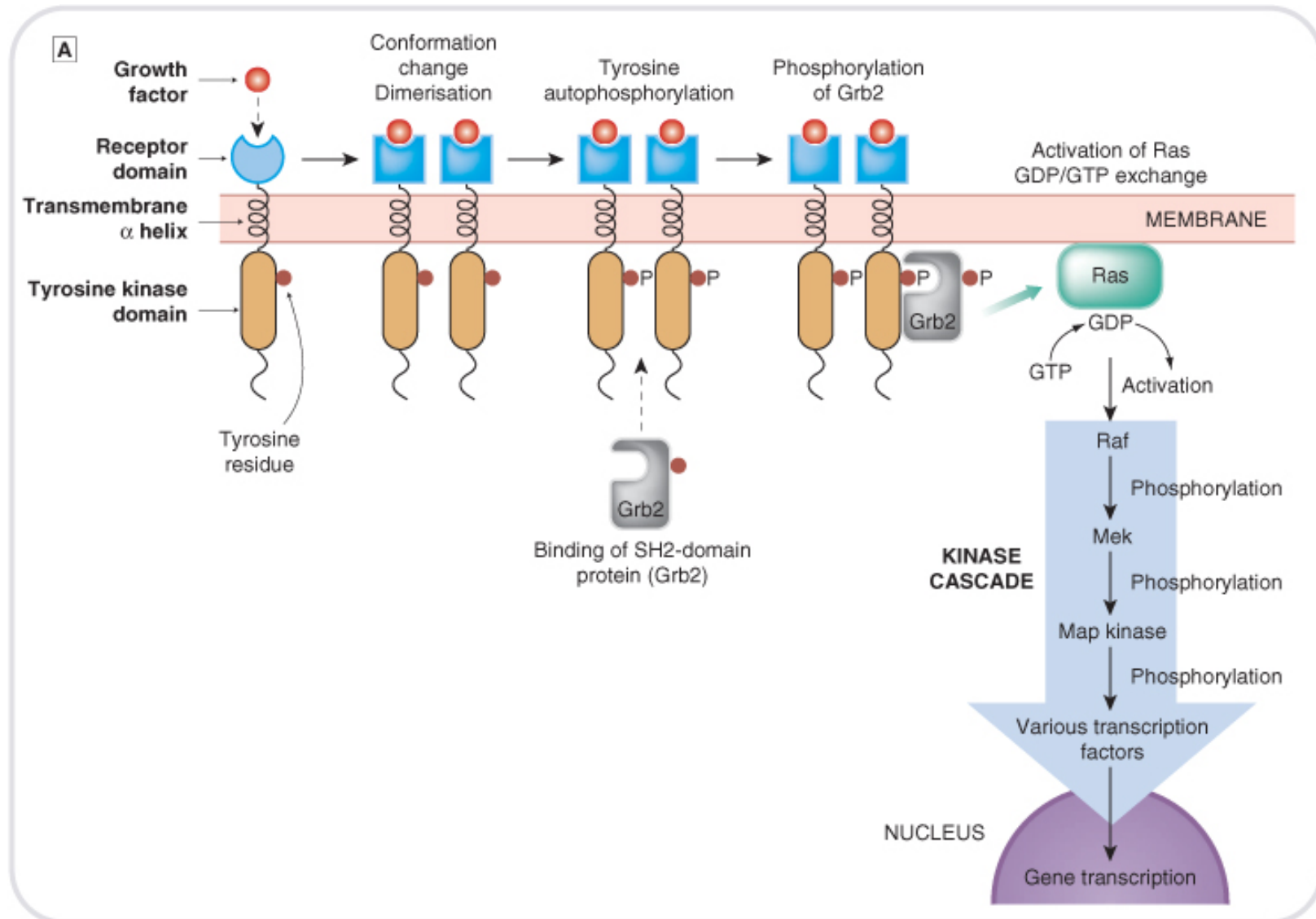
Typical tyrosine kinase cascade



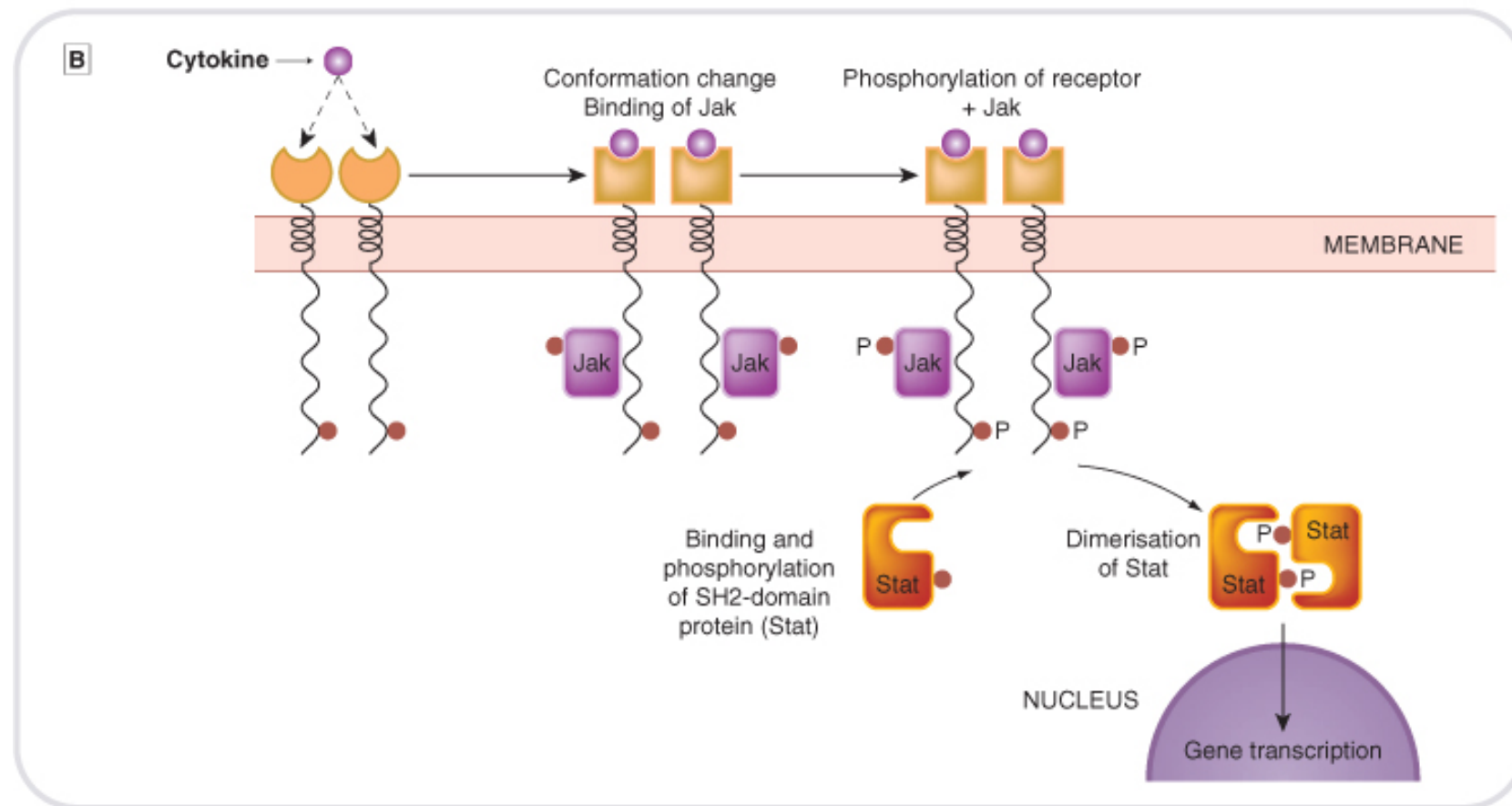
Agonist binding to 2 receptors leads to coupling (dimerisation). The TKs in each receptor phosphorylate the other member of the dimer

SH2-containing 'adapter' proteins bind to the phosphorylated residues in the receptors and activate a pathway consisting of Ras, which becomes activated after exchange of GDP for GTP; this, in turn, activates a cascade of three kinases. The last kinase phosphorylates various transcription factors, thus activating transcription of the genes for proliferation and differentiation

Growth factor cascade

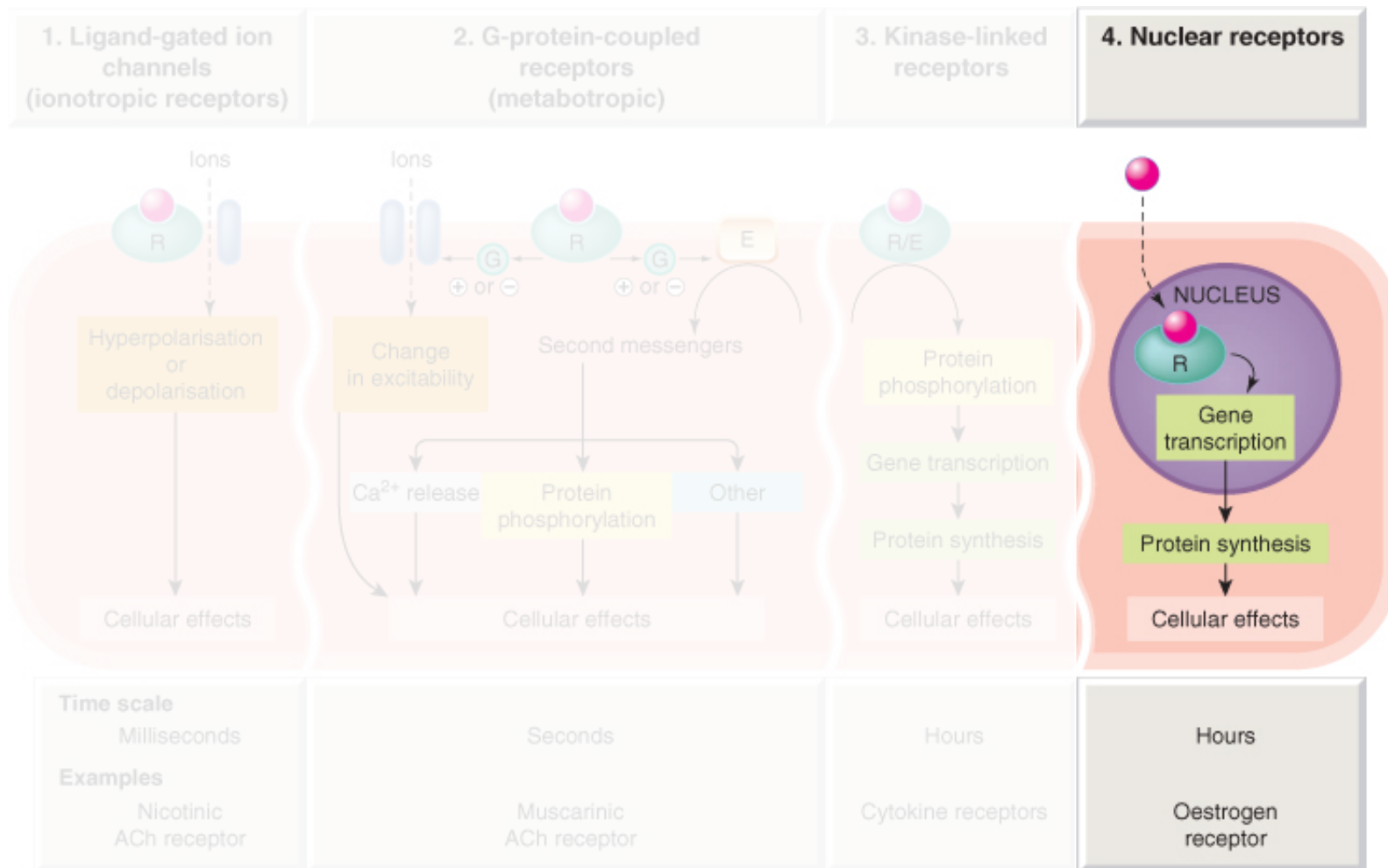


Cytokine receptor cascade



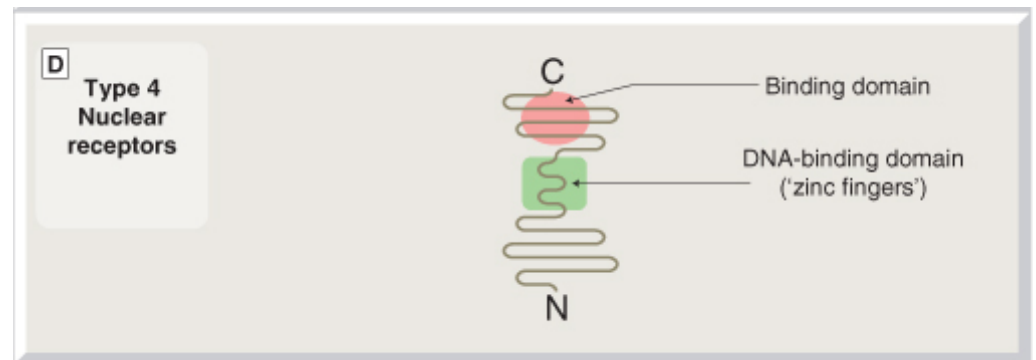
Type 4: Nuclear Receptors

Type 4: Nuclear Receptors



Nuclear Receptors

- Intracellular receptors affecting gene transcription
- Respond within hours
- Large family of proteins:
 - Monomeric
 - DNA binding domain “zinc fingers”
- Examples:
 - Thyroid hormone receptor
 - Steroid receptors



Examples of molecules binding nuclear receptors

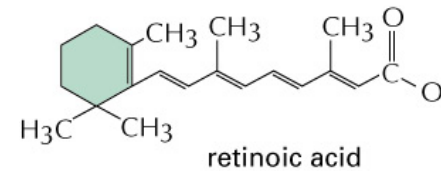
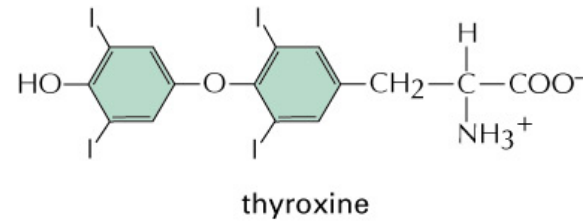
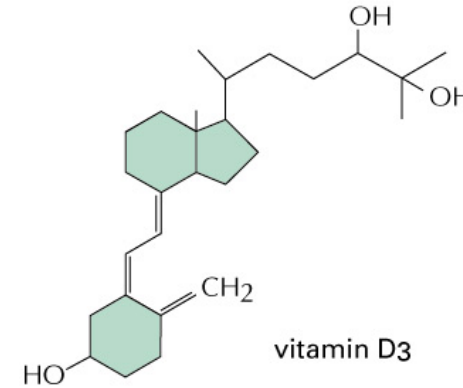
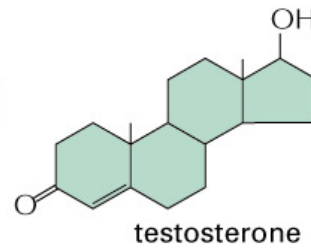
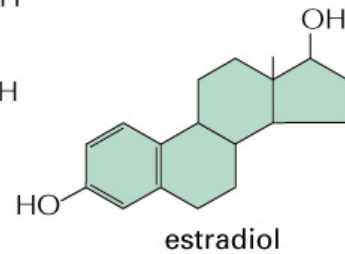
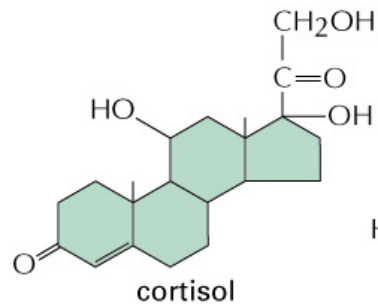


Figure 15-12 part 1 of 2. Molecular Biology of the Cell, 4th Edition.

Figure 15-12 part 2 of 2. Molecular Biology of the Cell, 4th Edition.

The Nuclear Receptor superfamily (1)

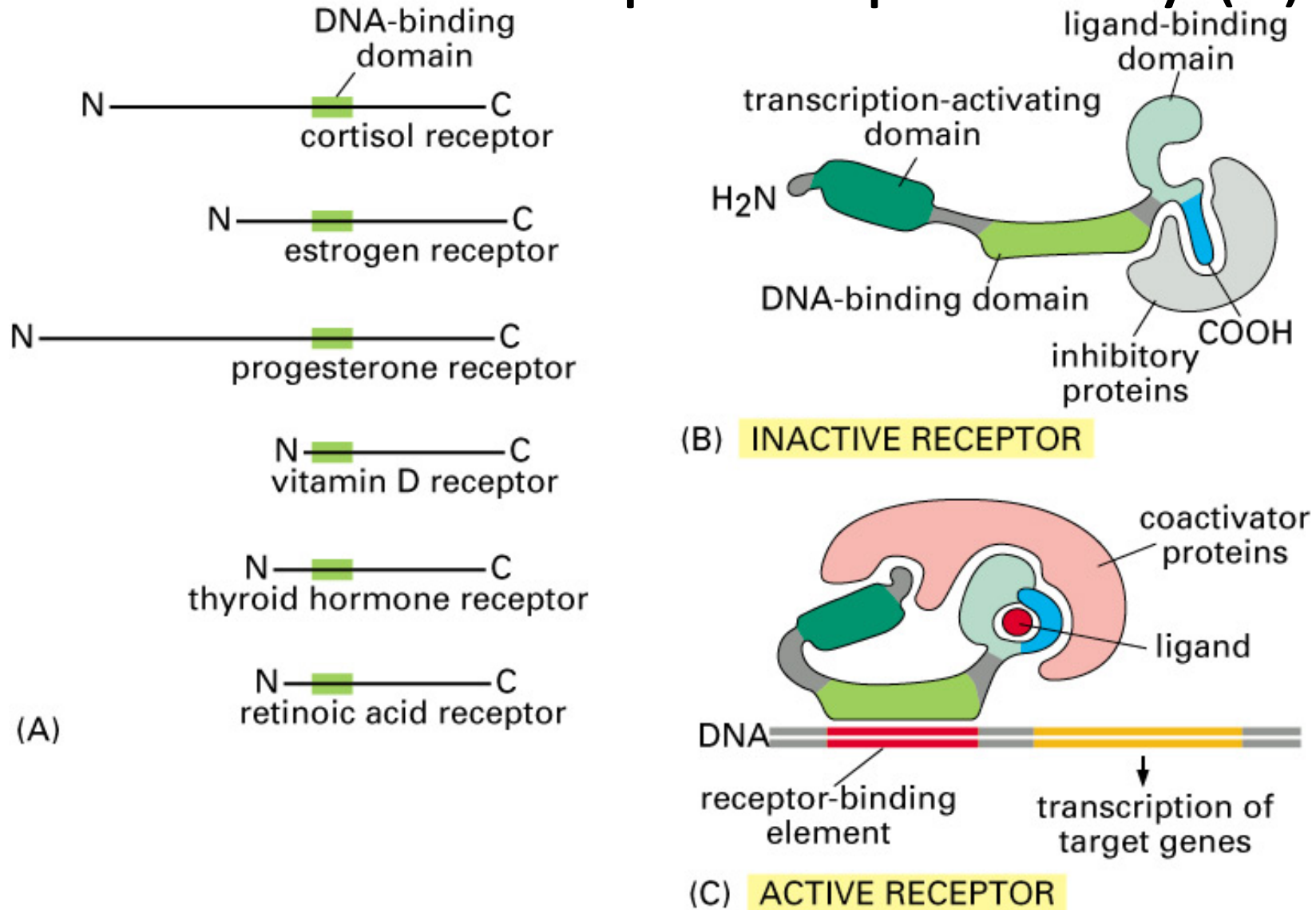
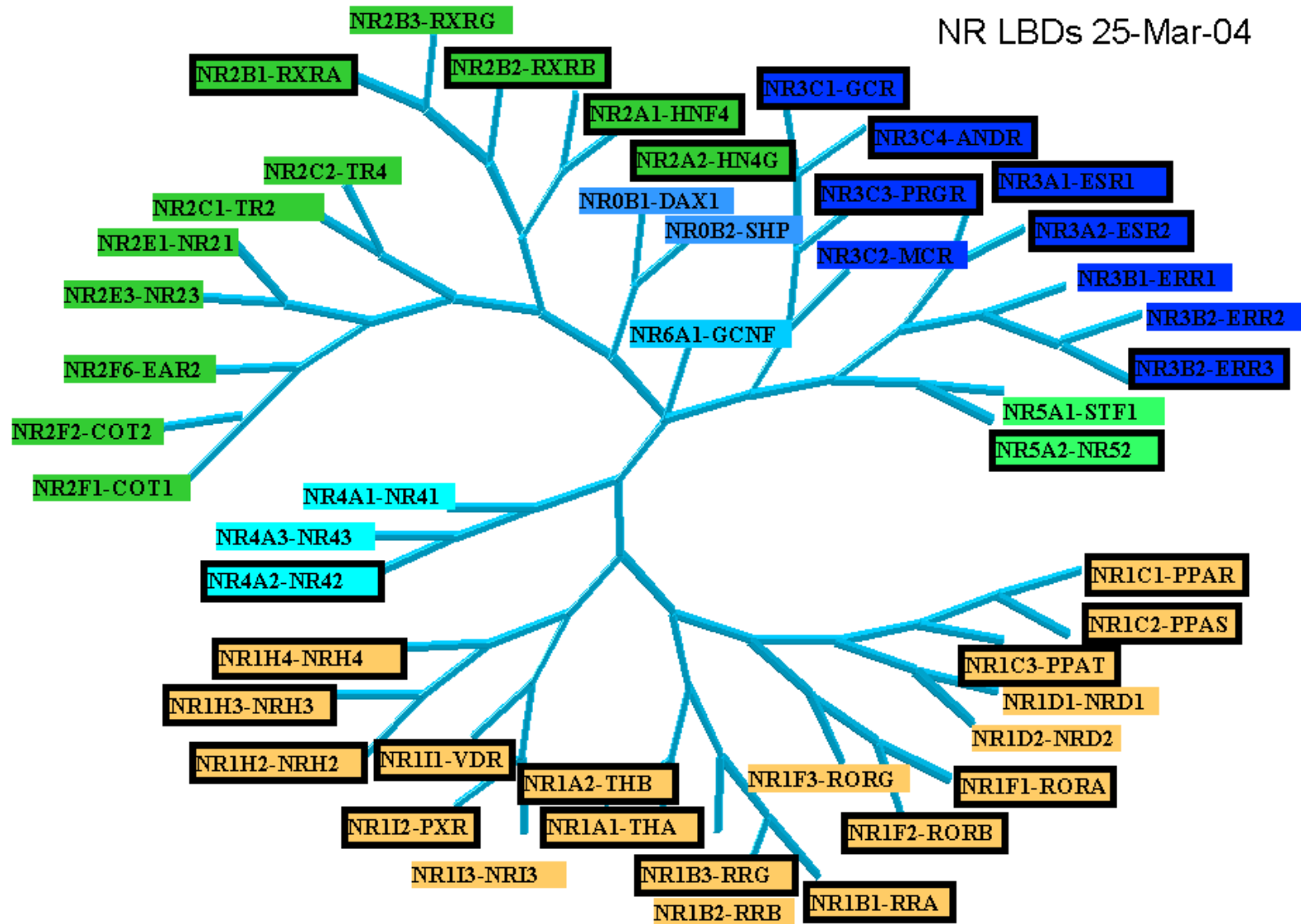
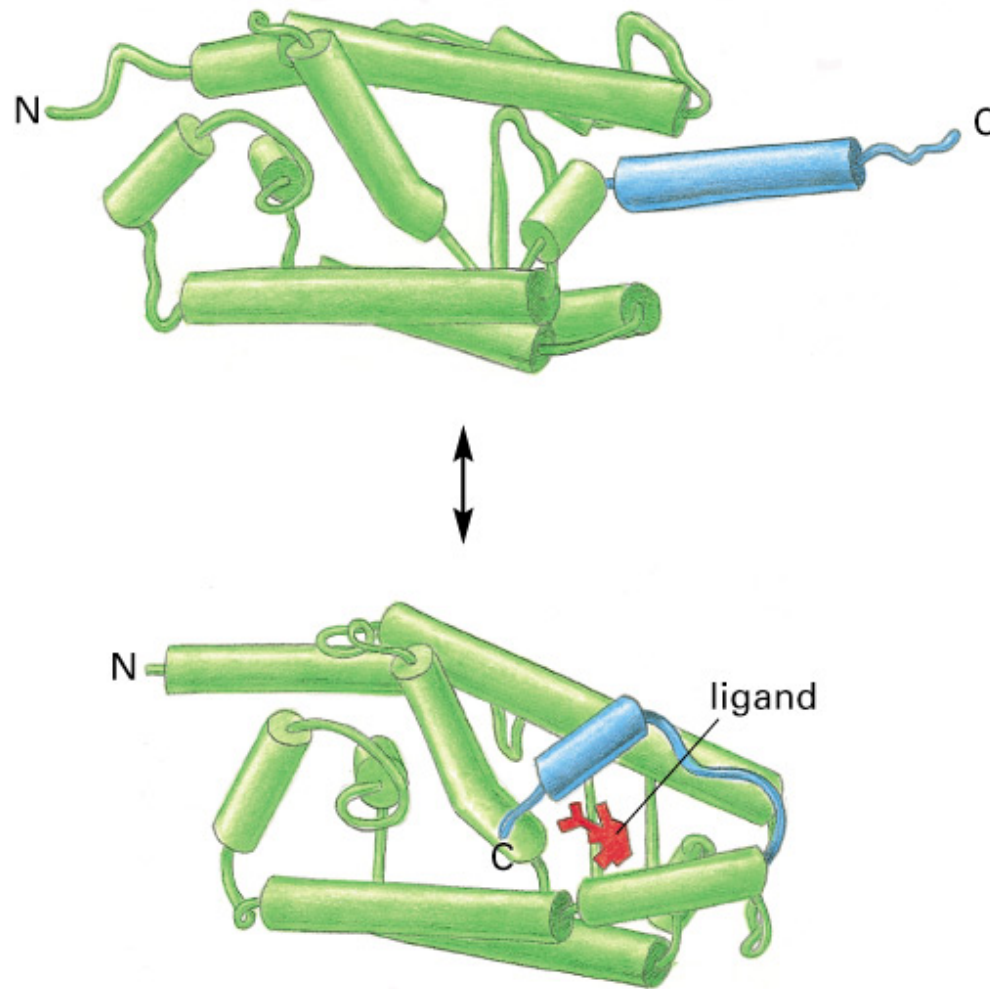


Figure 15–13 part 1 of 2. Molecular Biology of the Cell, 4th Edition.

The Nuclear Receptor superfamily (2)



3D structure of Nuclear Receptors



(D)

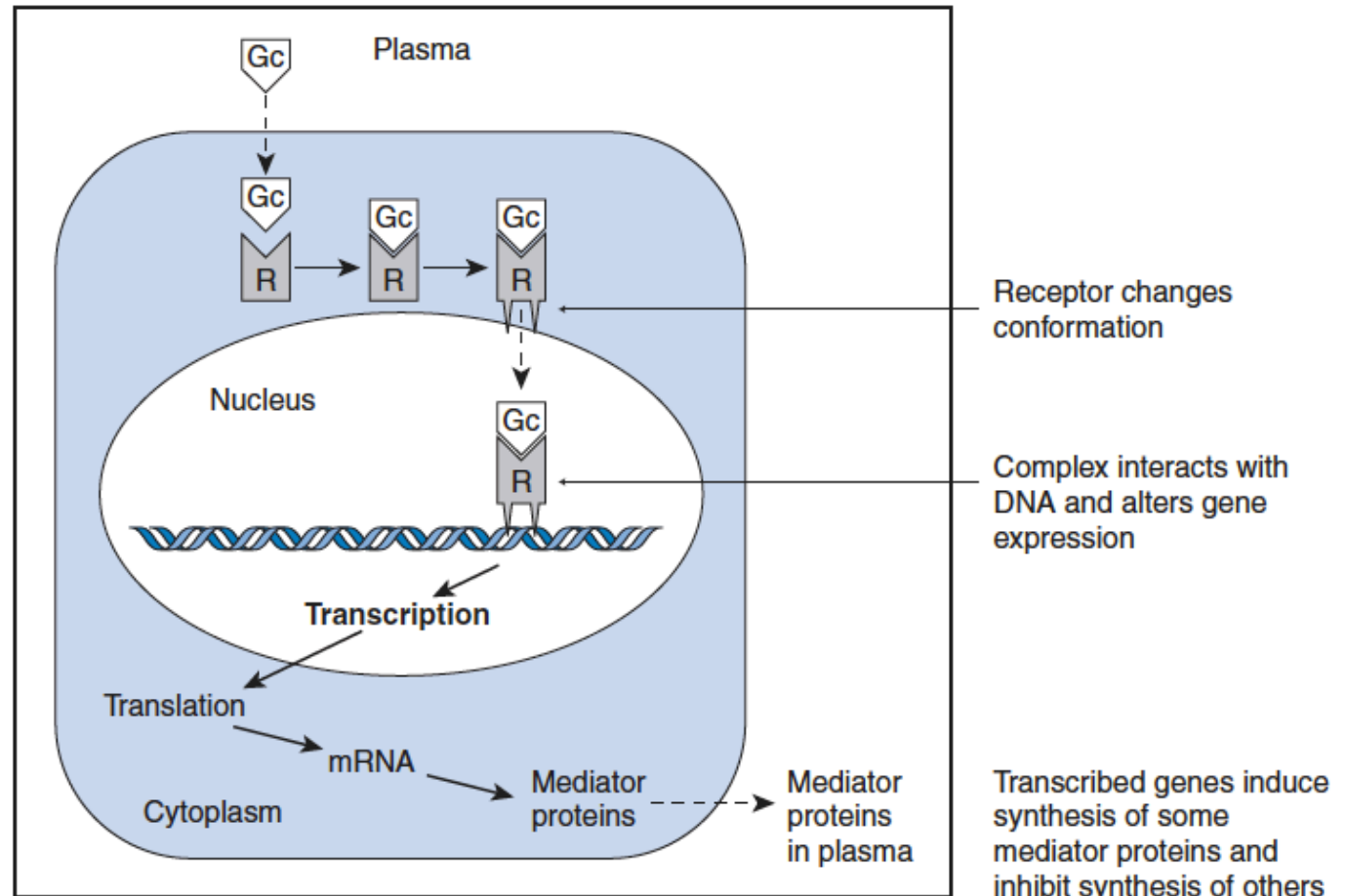
Figure 15–13 part 2 of 2. Molecular Biology of the Cell, 4th Edition.

Generic Nuclear Receptor Mechanism

Examples are members of the steroid superfamily of receptors;

- corticosteroid receptors
- oestrogen and progesterone receptors
- thyroid hormone receptors
- Vitamin D₃ receptors

The Gc/receptor complexes form dimers before entering the nucleus (not shown)



Two types of responses

(A) EARLY PRIMARY RESPONSE TO STEROID HORMONE

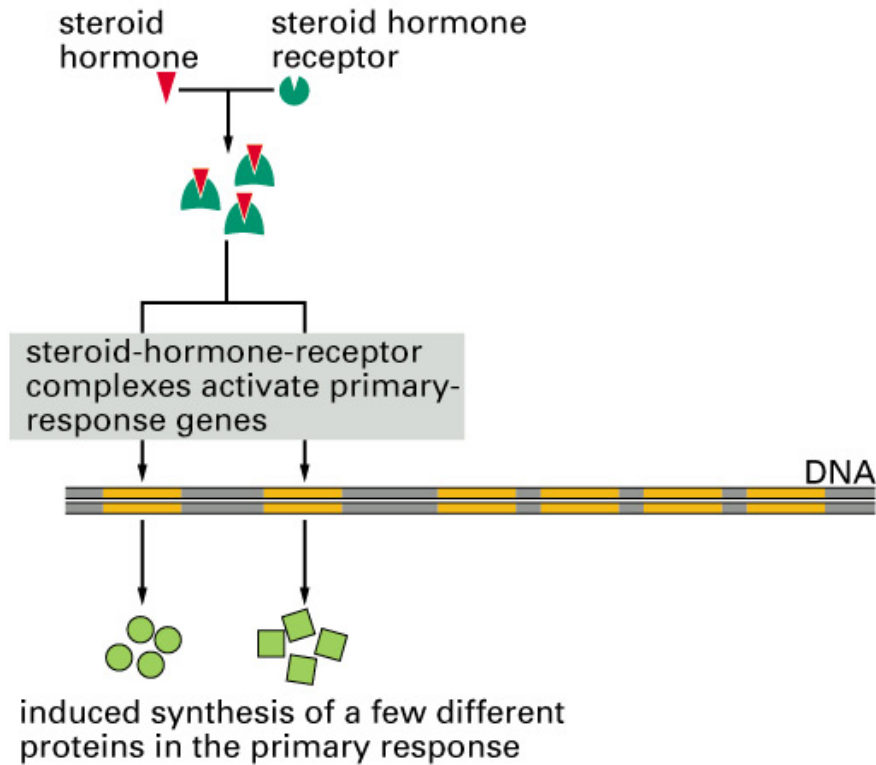


Figure 15–14 part 1 of 2. Molecular Biology of the Cell, 4th Edition.

(B) DELAYED SECONDARY RESPONSE TO STEROID HORMONE

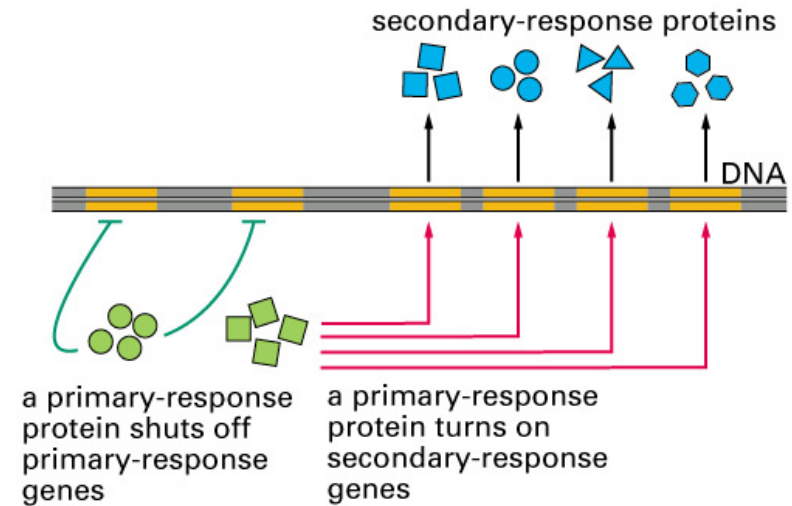
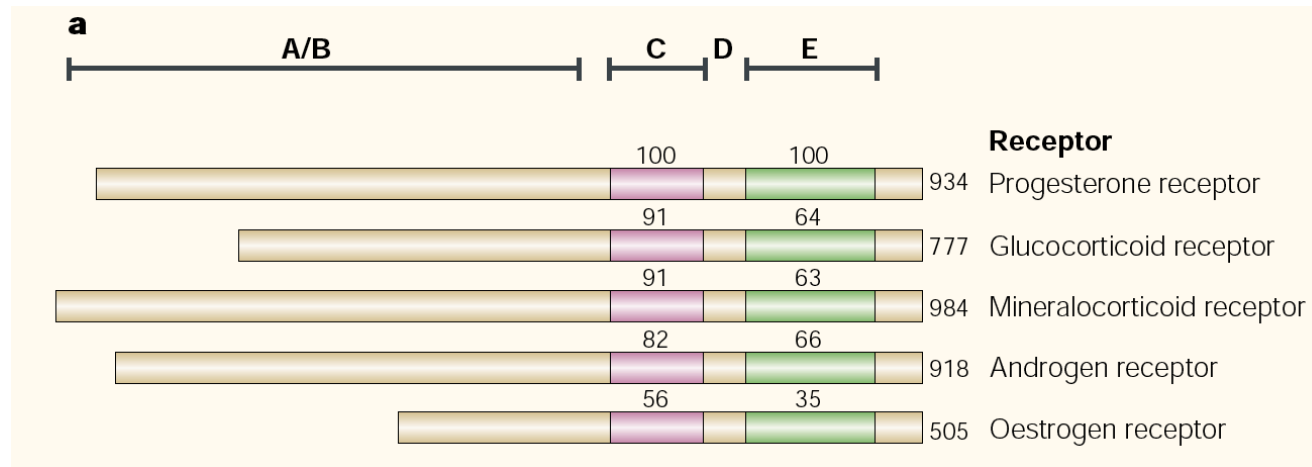
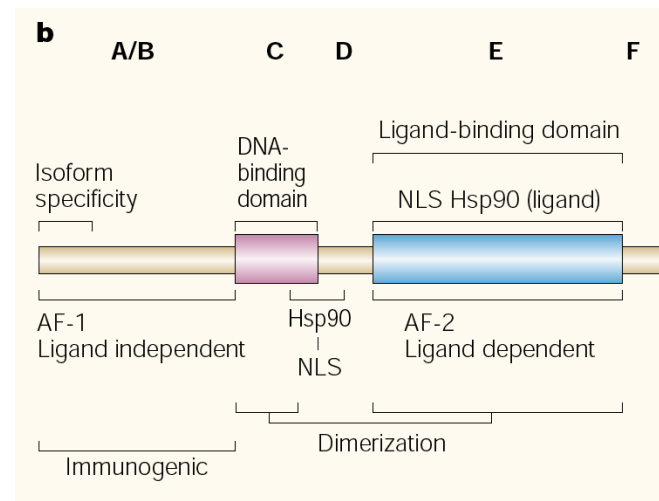


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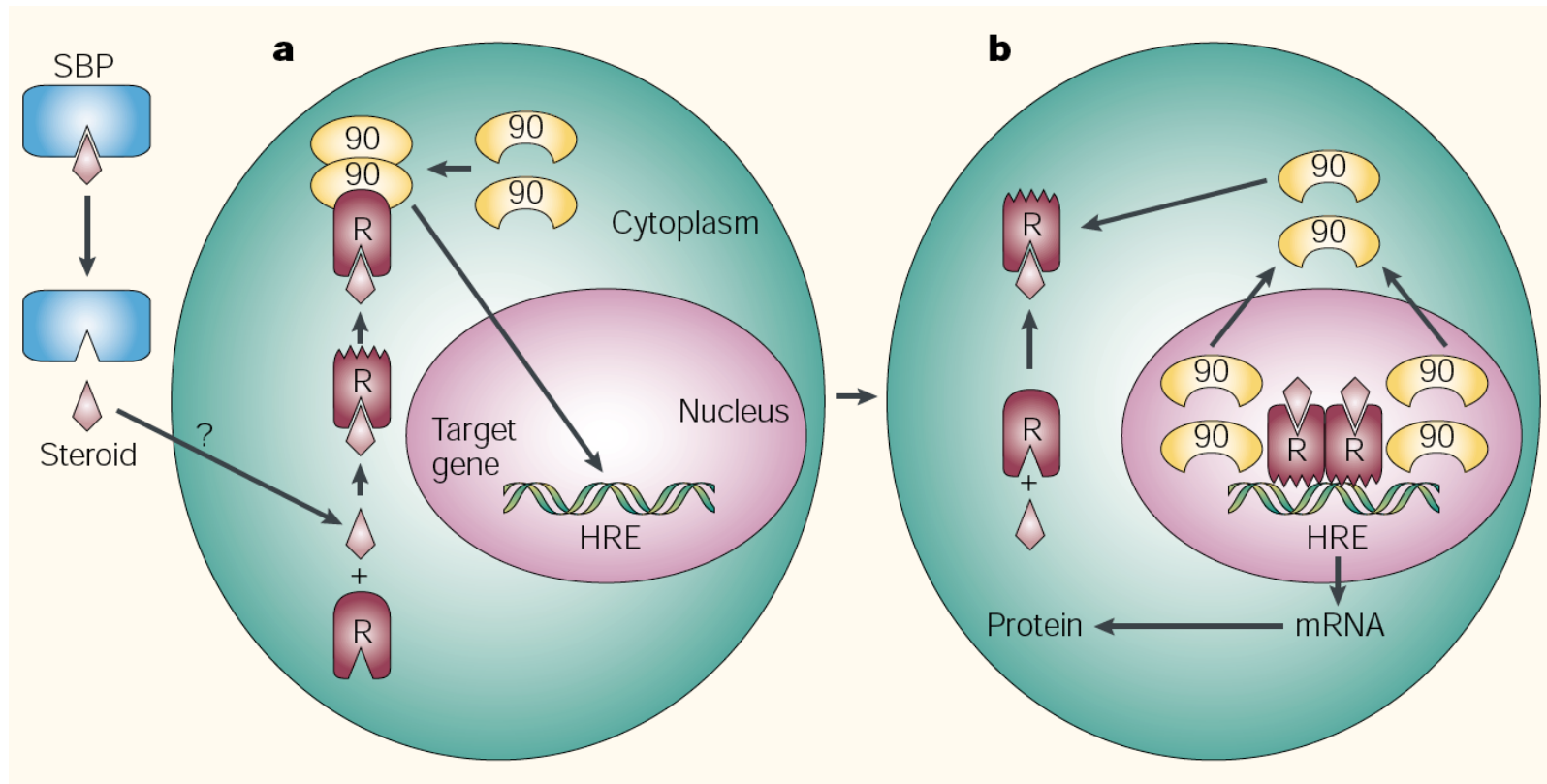
Steroid hormone receptors



- The relative sizes of the human receptors indicated.
- The numbers above the bars indicate the percentage homology of the consensus regions of the DNA- and ligand-binding domains

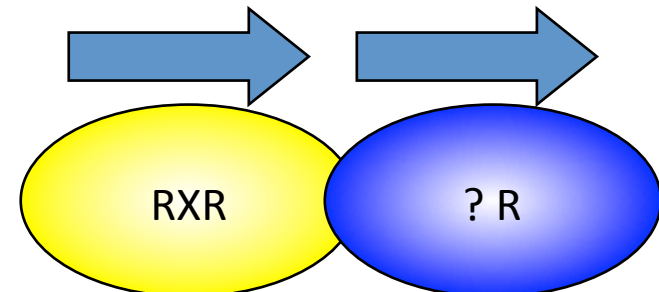


Mechanism of action SHR

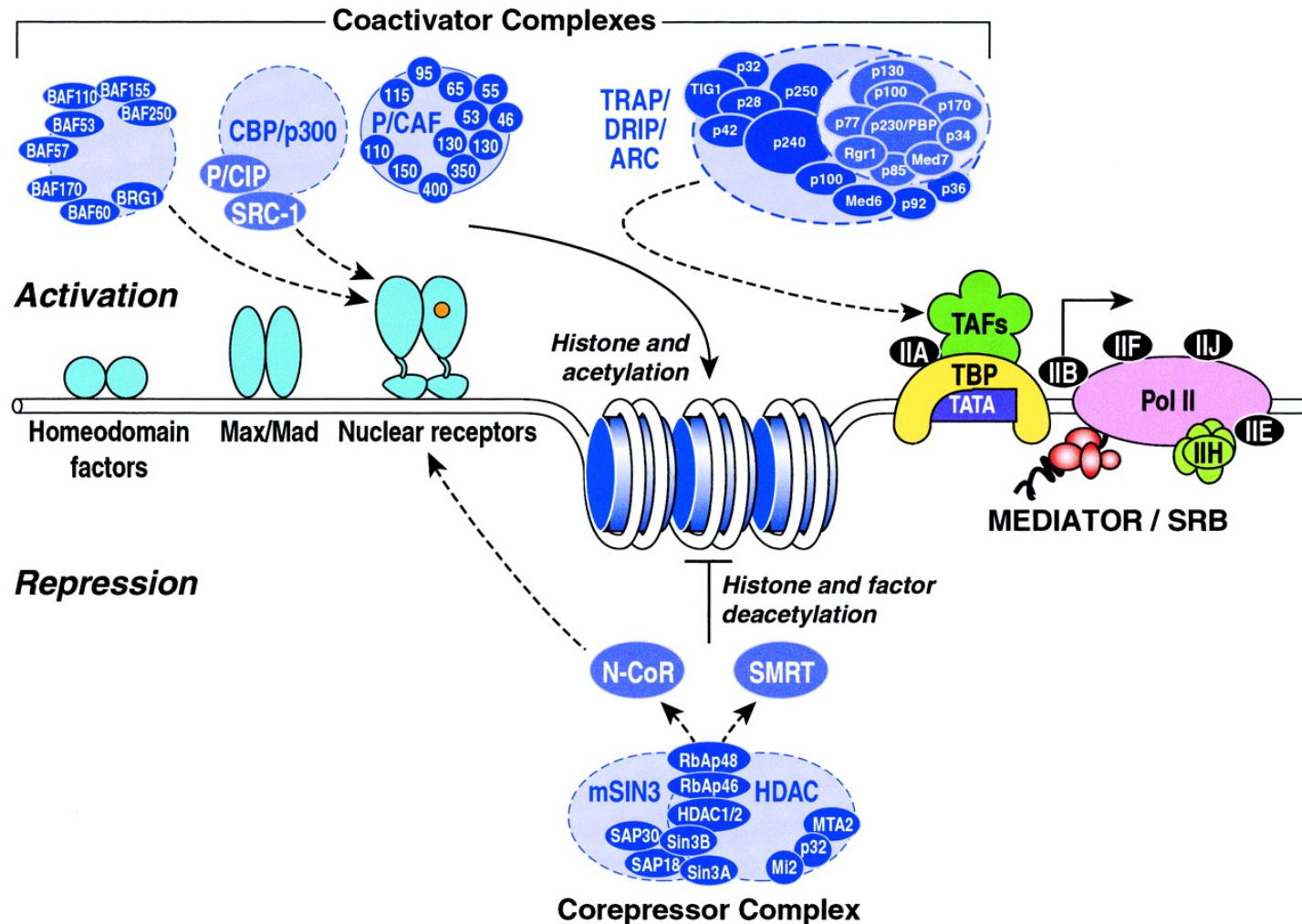


Sub-family: RXR heterodimers

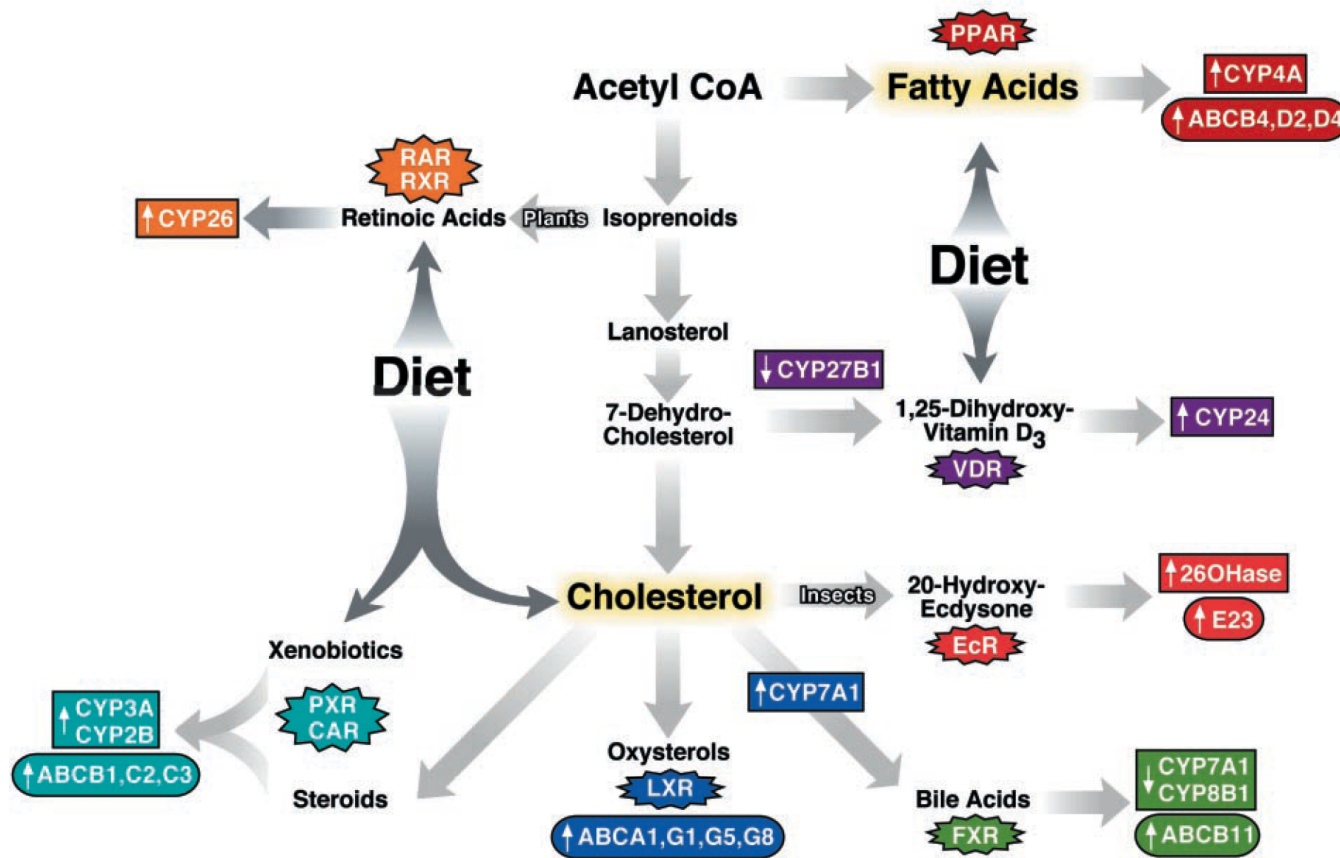
- Prototypiske members:
 - **RAR** [retinoic acid receptor] vitamin A metabolite
 - **VDR** [vitamin D receptor]
 - **TR** [thyroid hormone receptor]
 - **PPAR γ** [prostaglandine J2]
 - several “Orphan receptors” with unknown ligand
- Characteristic feature of the RXR-heterodimers
 - Broader chemical variation of ligands
 - Not all ligands are endocrine hormones
 - ligand-independent activation mechanisms exist
 - bind DNA also in absence of ligand
 - bind often to “direct repeats”
 - bind as heterodimers



Several coactivators and corepressors

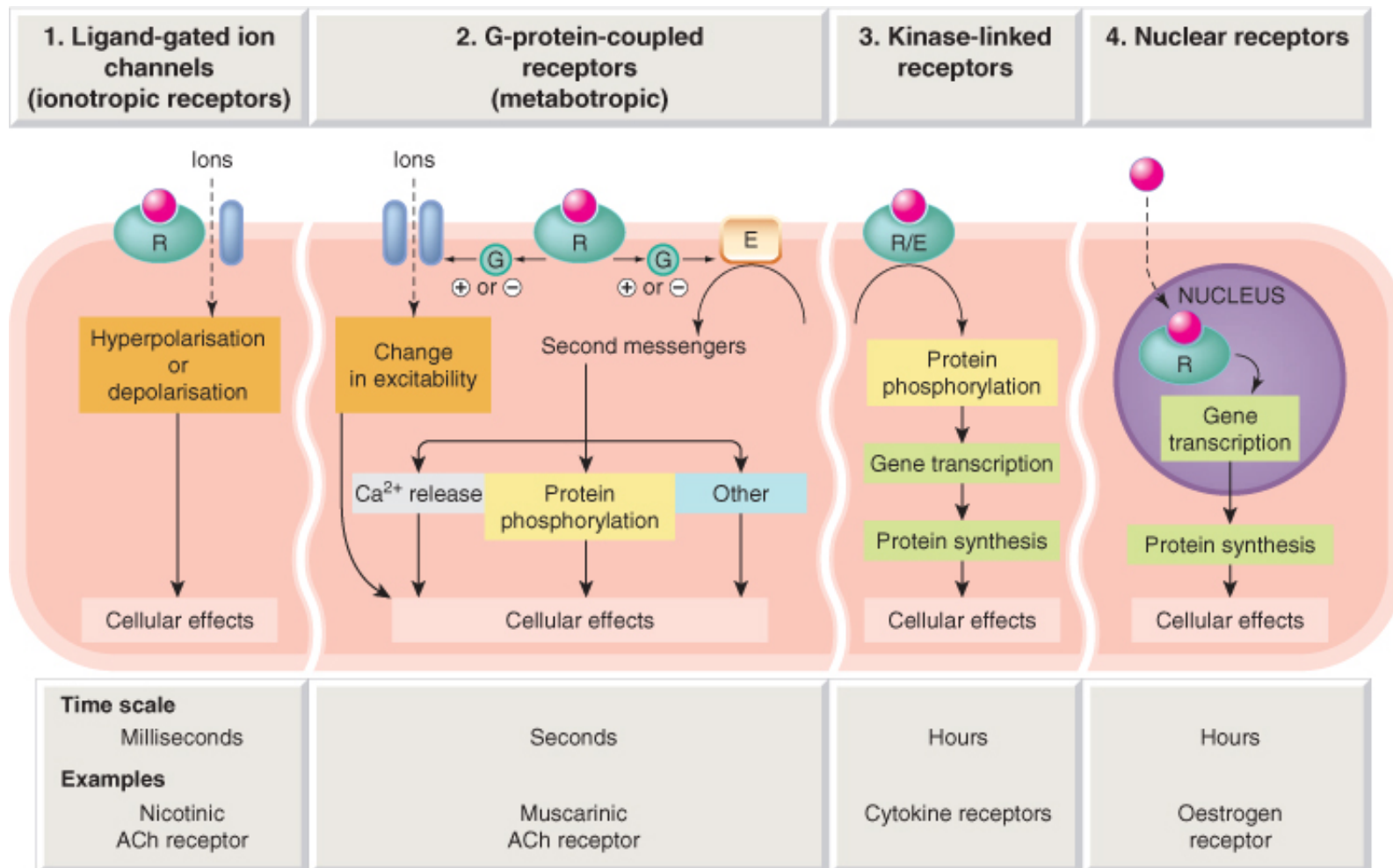


Bioactive lipids and their nuclear receptors

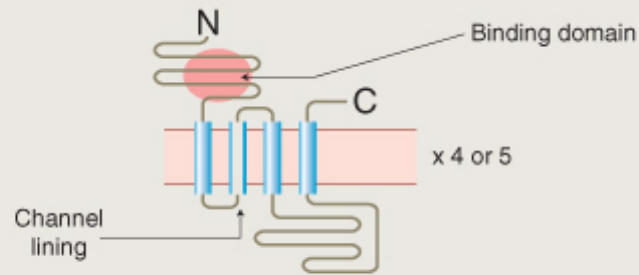


Nuclear receptor	Ligand
Retinoid X receptors*	RXR α,β,γ 9- <i>cis</i> Retinoic acid
Peroxisome proliferator-activated receptors	PPAR α Fatty acids Fibrates
	PPAR δ Fatty acids Carboprostacyclin
	PPAR γ Fatty acids Eicosanoids Thiazolidinediones
Liver X receptors	LXR α,β Oxysterols
Farnesoid X receptor	FXR Bile acids
Xenobiotic receptors	SXR/PXR Xenobiotics Steroids
	CAR Xenobiotics Phenobarbital
Ecdysone receptor	EcR 20(OH)-ecdysone
Retinoic acid receptors	RAR α,β,γ Retinoic acids
Vitamin D receptor	VDR 1,25(OH) ₂ -vitamin D ₃

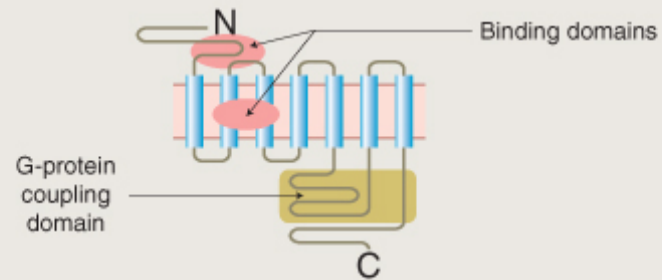
Receptors: synopsis



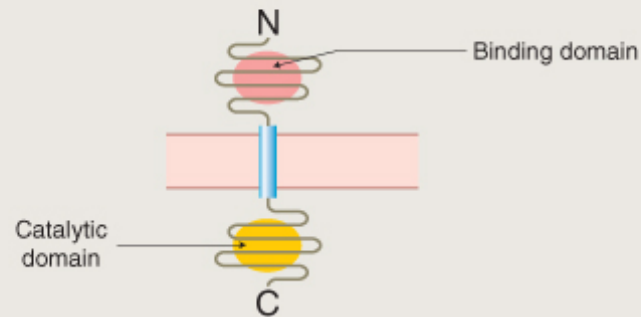
A
Type 1
Ligand-gated
ion
channels
(ionotropic
receptors)



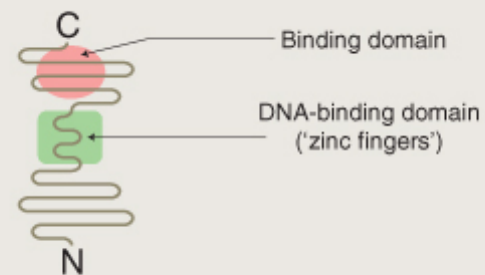
B
Type 2
G-protein-
coupled
receptors
(metabotropic
receptors)



C
Type 3
Kinase-linked
receptors



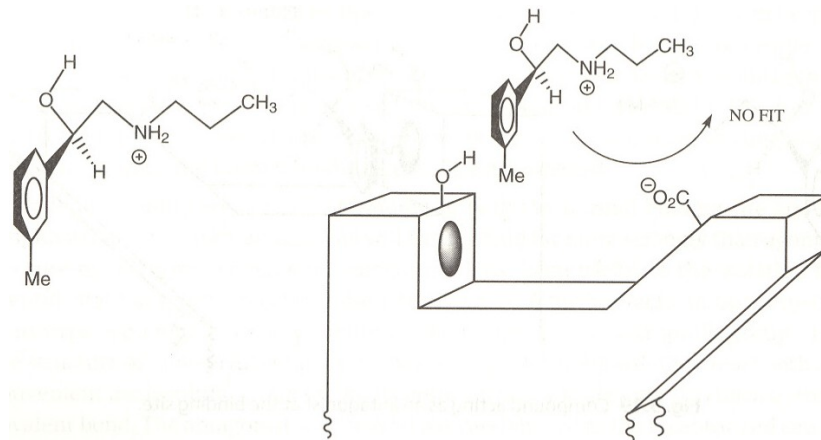
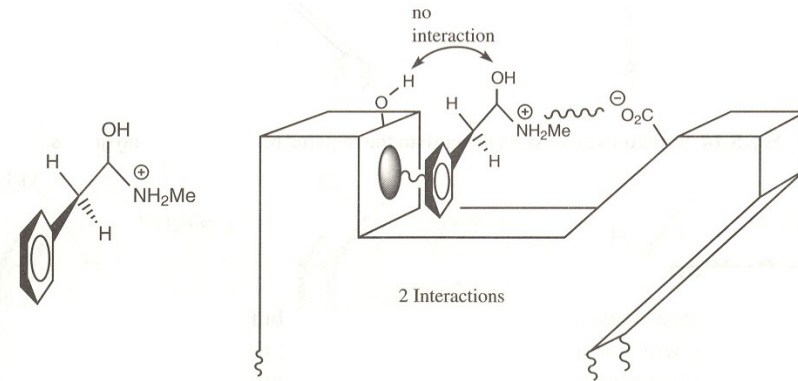
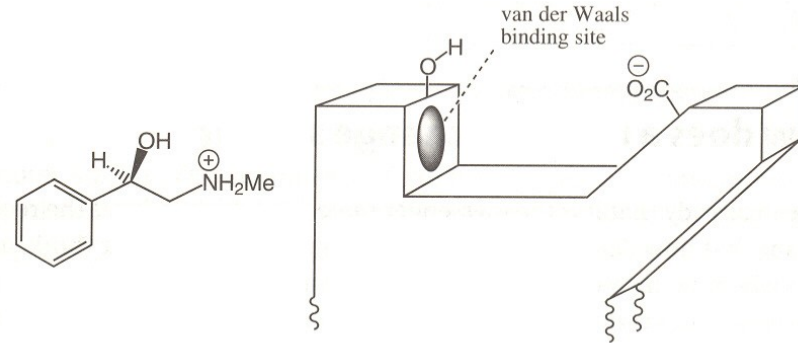
D
Type 4
Nuclear
receptors



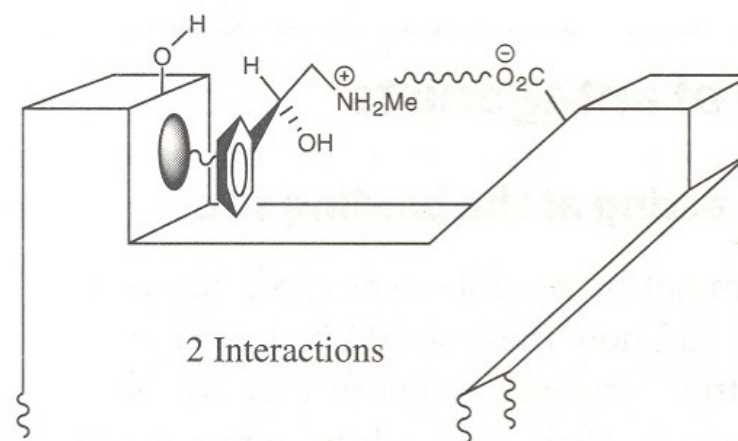
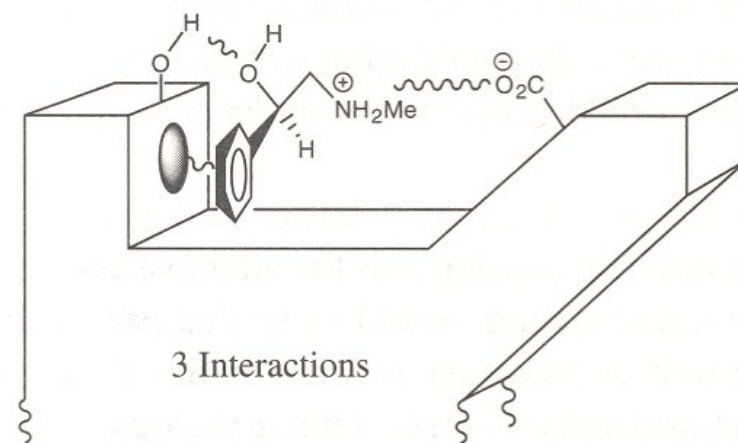
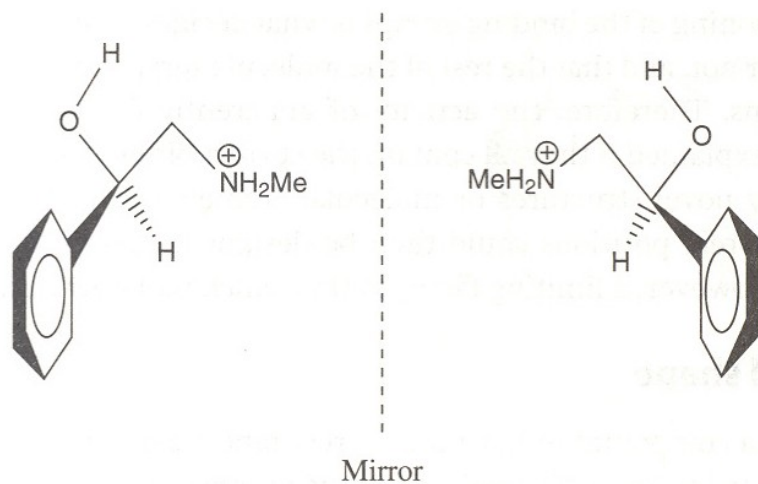
How drugs interact with receptors

Agonists

- Receptor binding site
- Design of agonist:
 1. Correct binding groups
 2. Correctly positioned
 3. Correct size

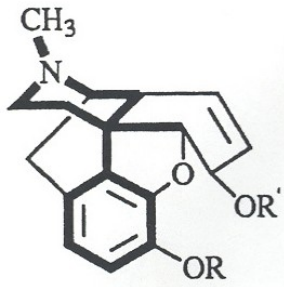


Enantiomers

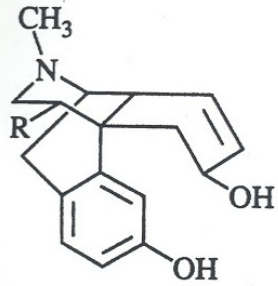


- Asymmetrical Synthesis

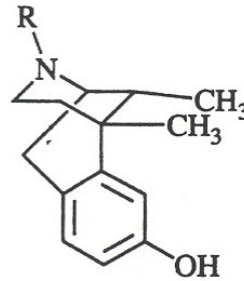
Pharmacophore



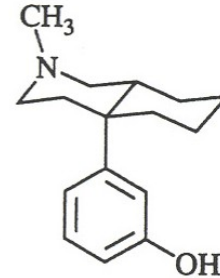
2.19



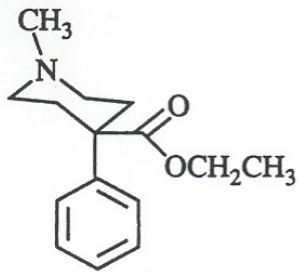
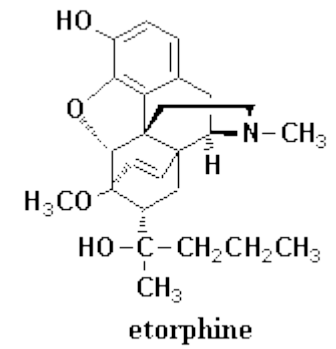
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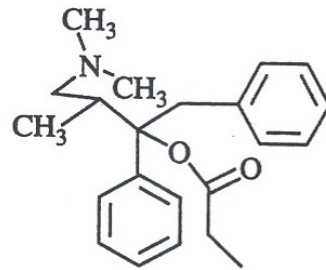
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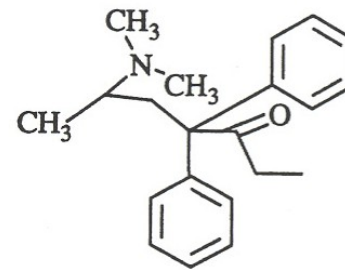
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2.23

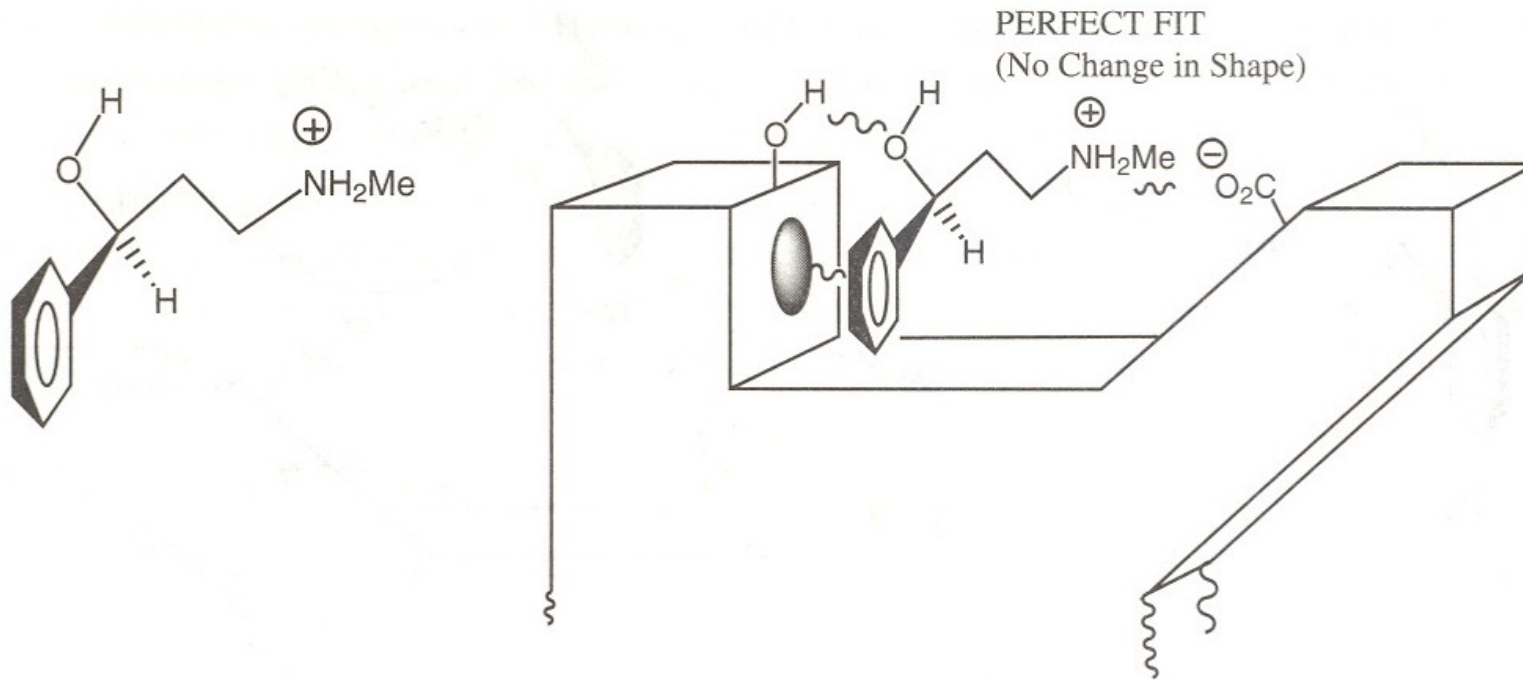


2.24



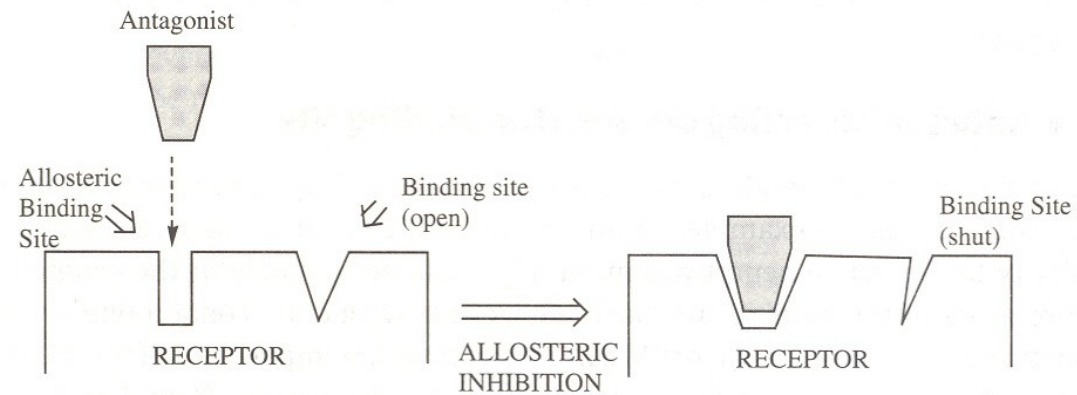
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Antagonists

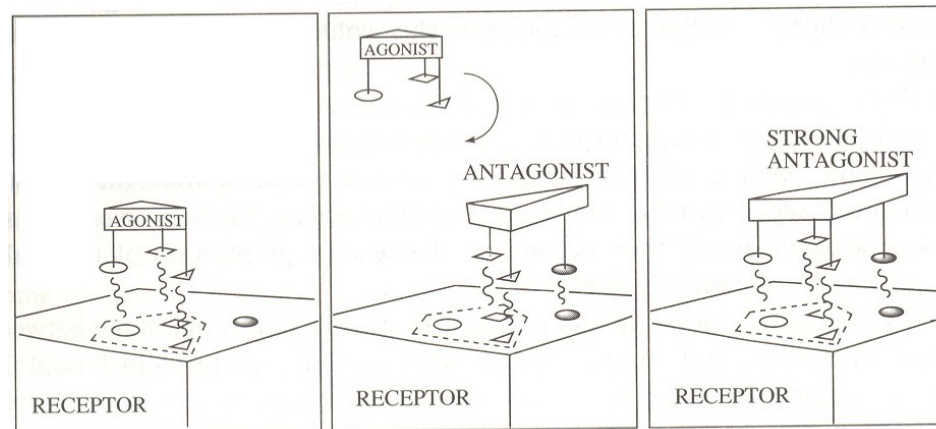


Other types of antagonists:

- Allosteric antagonists

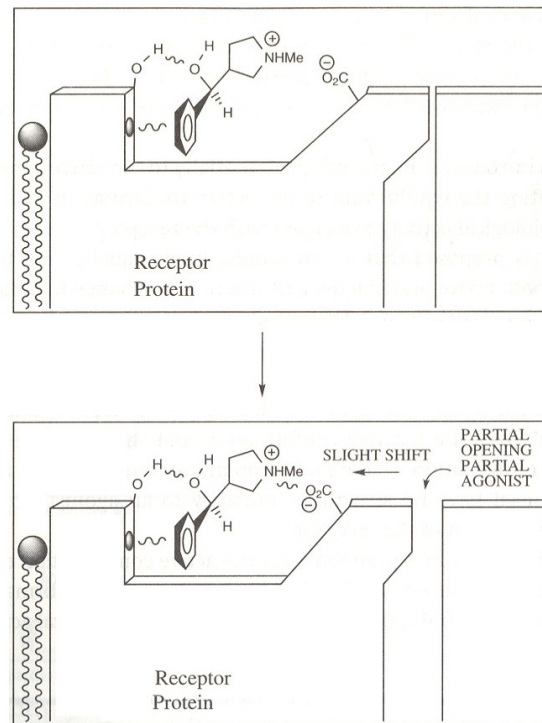


- Antagonism by the umbrella effect



Partial agonists

1. Small conformational change



2. Multiple binding, same receptor

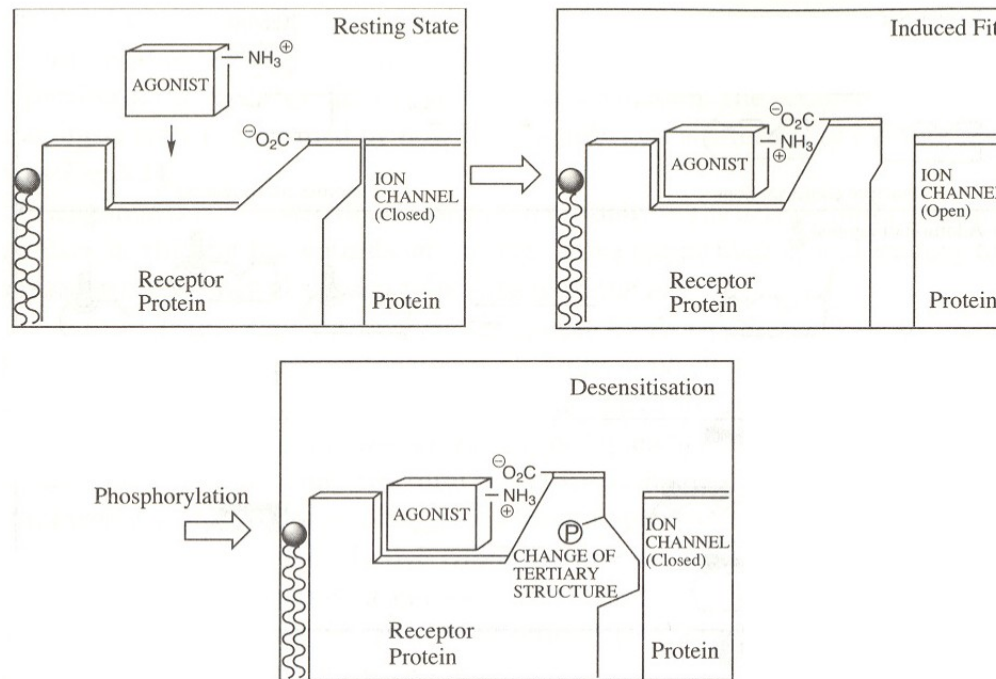
3. Multiple receptors

After binding...

- What happens when a drug binds to the receptor and stays for a prolonged period of time?
 1. Desensitization
 2. Sensitization

1. Desensitization

- Phosphorylation



- Endocytosis
- Reduction of receptors

2. Sensitization

- Prolonged deactivation by antagonist leads to deficiency of messages sent to cell
- Leads to *tolerance* and *dependence*

