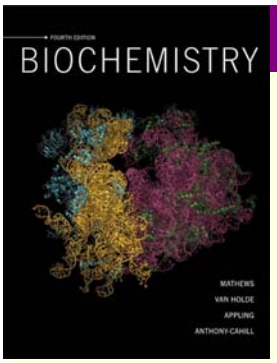
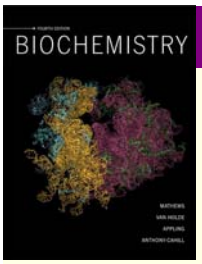


Chapter 23

Cell Communication and Biosignaling (L12, M23, Lodish 15 16)

生化分生科 游佳融

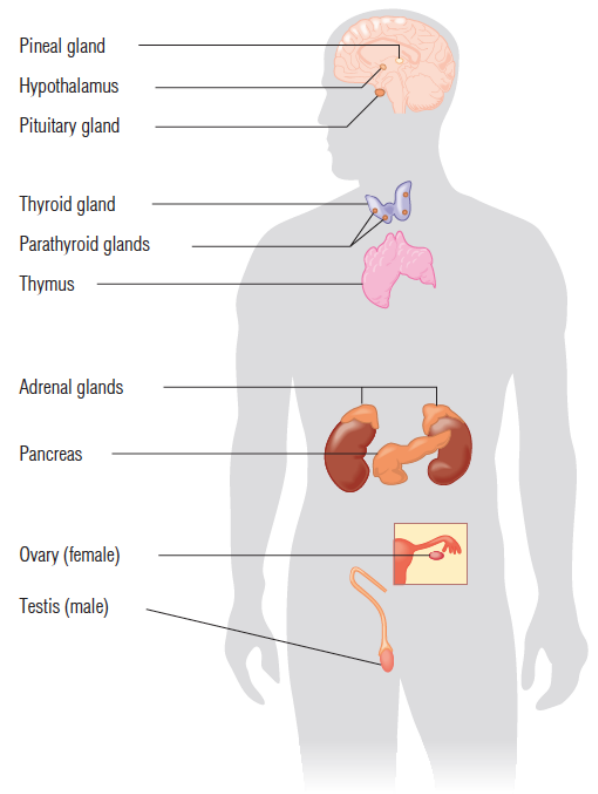
2015/01



Chapter 23 Outline:

- An Overview of Hormone Action
- Hierarchical Nature of Hormonal Control
- Signal Transduction: Receptors
- Transducers: G Proteins
- Effectors: Adenylate Cyclase
- Second-Messenger Systems
- Receptor Tyrosine Kinases
- Steroid and Thyroid Hormones: Intracellular Receptors
- Signal Transduction, Oncogenes, and Cancer
- Neurotransmission
- Signaling in Bacteria and Plants

The major human endocrine glands and their central nervous system control centers



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Hierarchical Nature of Hormonal Control (I)

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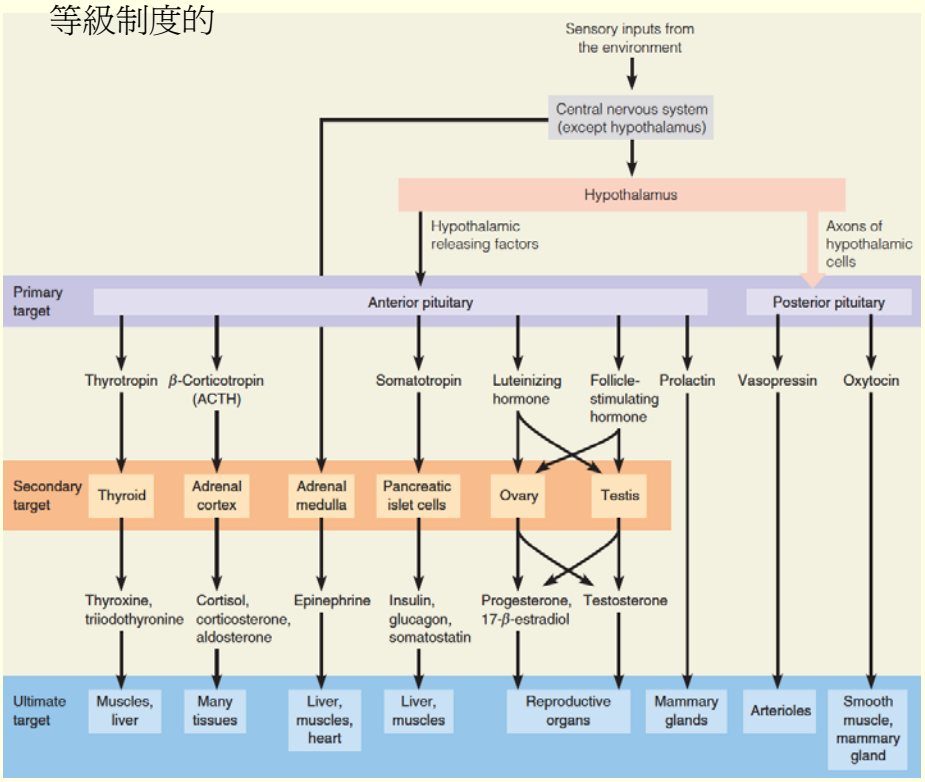
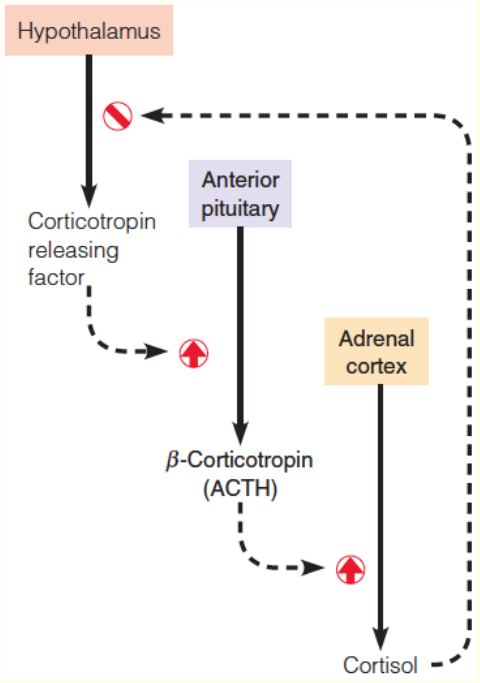


Hierarchical Nature of Hormonal Control (II)

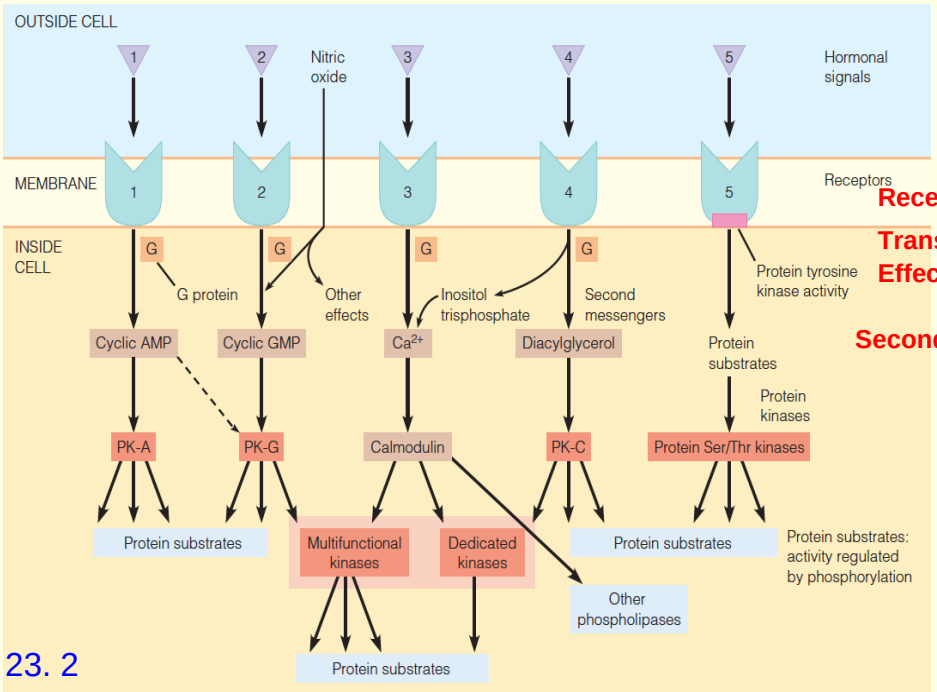
An example of feedback regulation of a hormone:

•Corticotropin releasing factor (CRF) stimulates the release of β-corticotropin (ACTH) from the anterior pituitary.

•ACTH stimulates the adrenal cortex to release cortisol, which feeds back on the hypothalamus to inhibit further release of CRF.



An Overview of Hormone Action



Receptor

Transducer

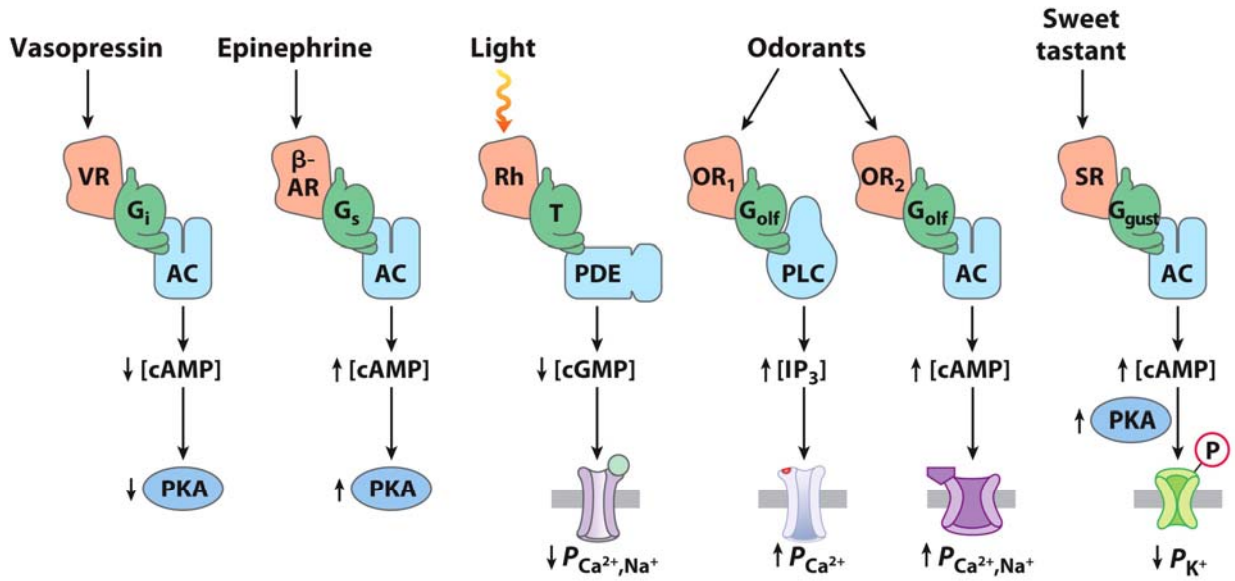
Effector (AC, Enz)

Second messengers

Eukaryotic signal transduction systems involving membrane receptors (1–5) and/or second messengers (1–4).

Sensory perception is mediated by G protein coupling receptor (GPCR)

感知能力



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補充 1

Transduction of the epinephrine signal: the β-adrenergic pathway

- Seven transmembrane segment receptor
- Heterotrimeric GTP-binding stimulatory G protein/Gs, GPCR

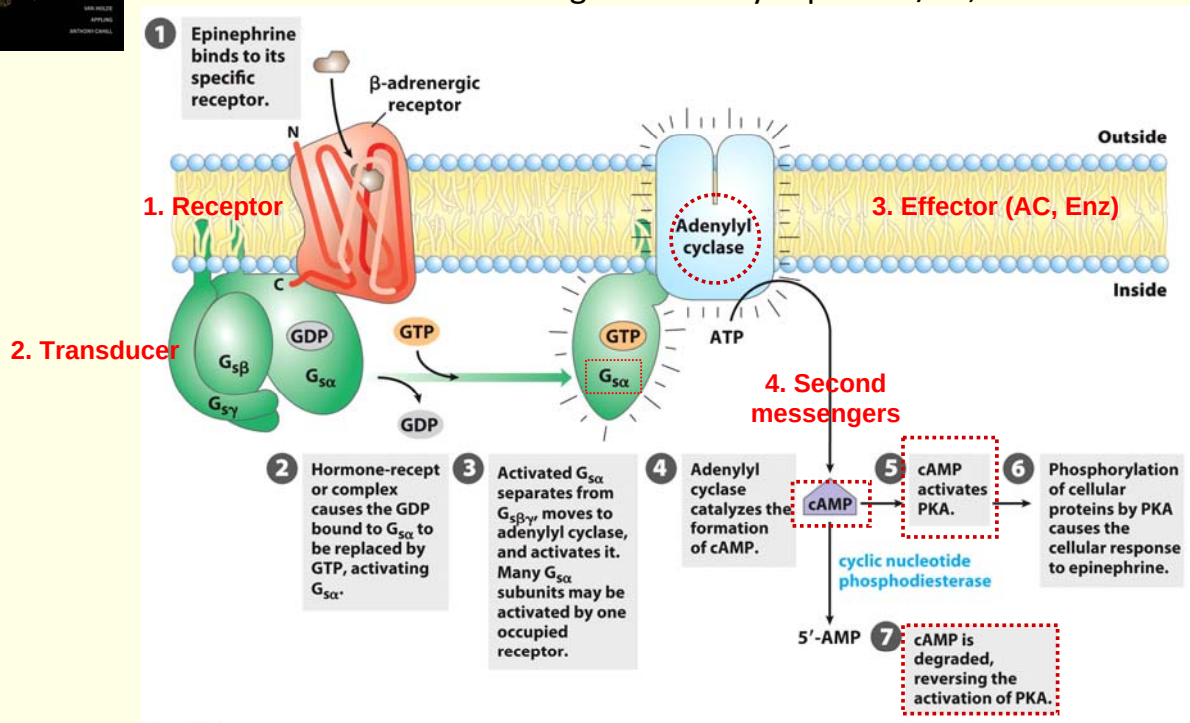

Figure 12-4a
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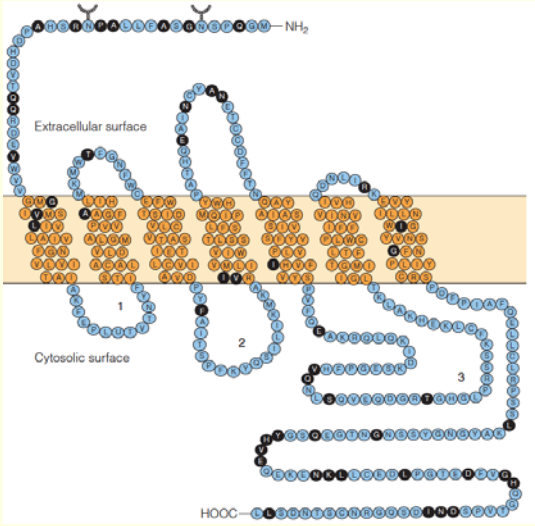
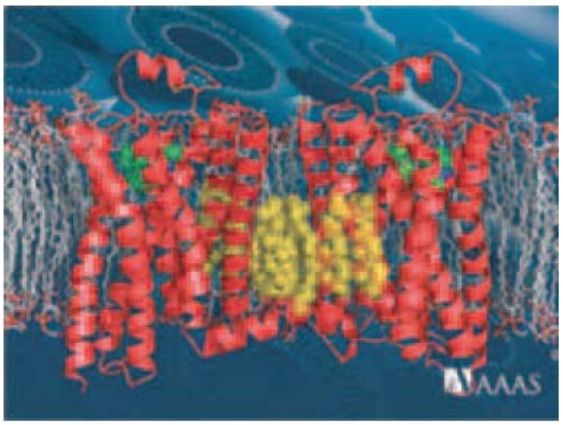
補充 2

Human β2-adrenergic receptor

- The seven conserved transmembrane domains are shown in orange.
- Interaction of the receptor with G proteins is controlled in part by reversible phosphorylation of serine and threonine residues near the *C*-terminus.

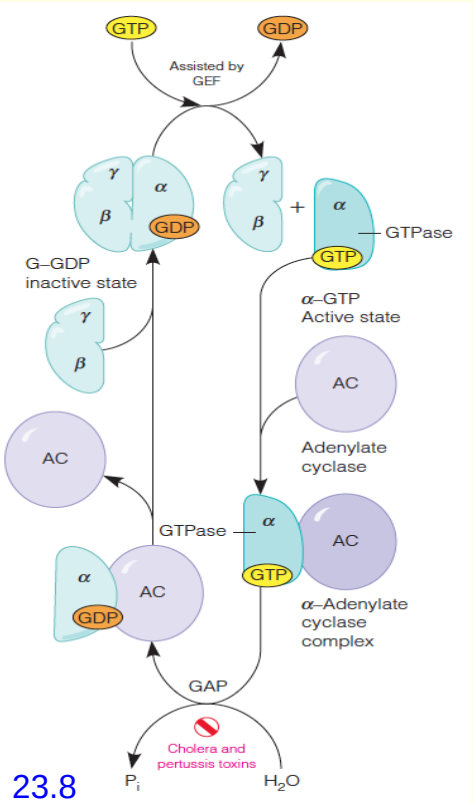


23.6



23.7 Green: ligand carazolol
Yellow: cholesterol molecules

Transducers: G Proteins



23.8

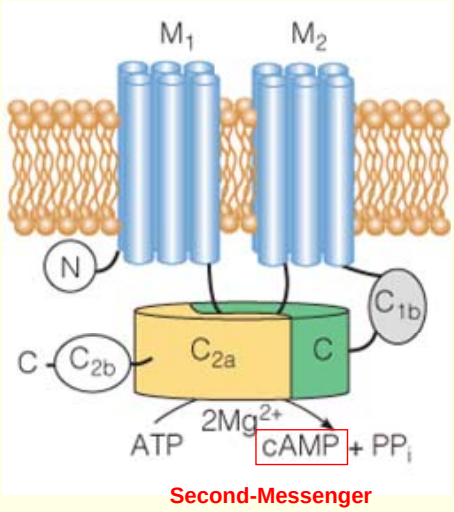
The cycle of G protein dissociation and reassociation:

- α, β, and γ are the three subunits of the G protein.
- The active form is the α–GTP complex.
- The sites of action of pertussis and cholera toxins are also shown.
- Gsα

Effectors: Adenylate Cyclase

➢Mammalian cells contain 10 AC isoforms that are regulated by heterotrimeric G proteins.

➢two transmembrane domains, M1 and M2, and two homologous cytoplasmic domains, C1 and C2.

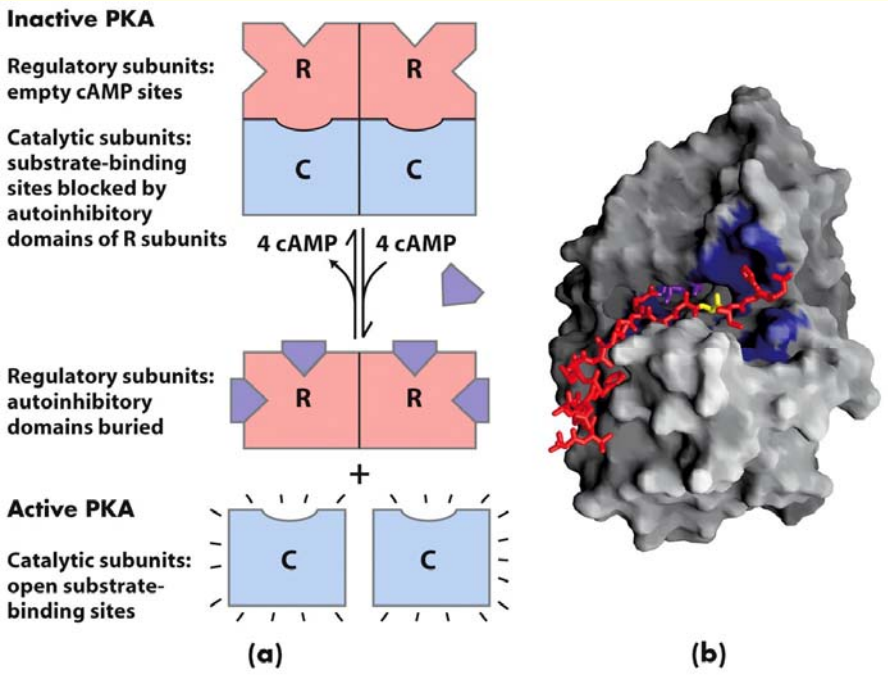


Second-Messenger

23.10

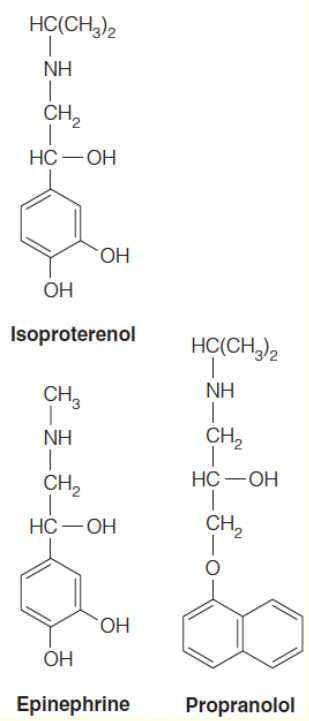
Activation of PKA (cAMP-dependent protein kinase)

➢**Allosterically activated by cAMP**



補充 3

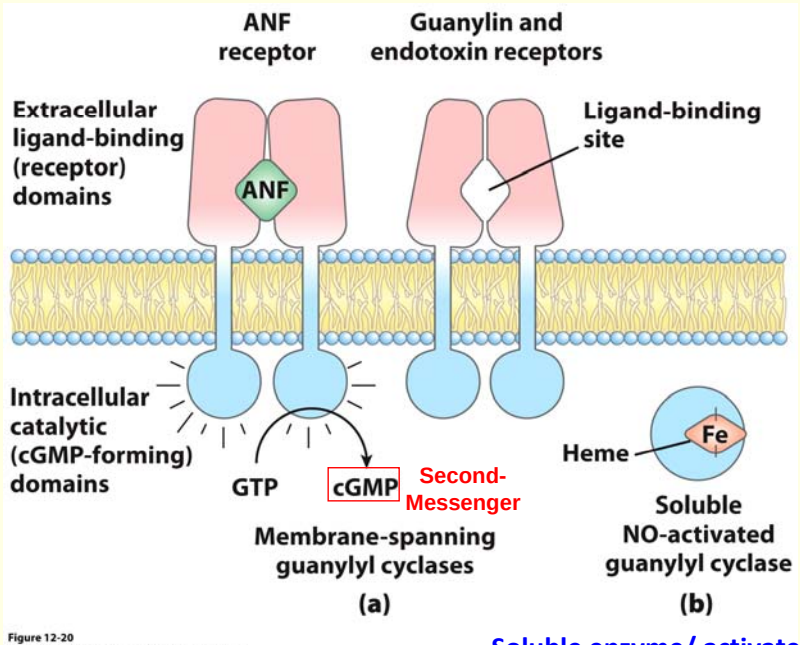
Agonist *vs.* Antagonist



- A hormone ***agonist*** mimics a hormone in binding productively to a receptor.
- A hormone ***antagonist*** binds nonproductively, inhibiting the action of the natural hormone.
- Propranolol is a β-adrenergic receptor antagonist.
- Epinephrine and isoproterenol are agonists.

Receptor Guanylyl Cyclases

- Catalytic domain converts GTP to cGMP
- Works through activation of protein kinase G
- ANF receptor/ atrial natriuretic factor (renal and blood vessel)



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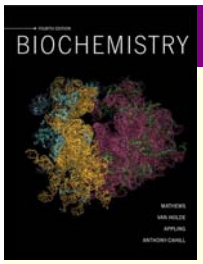
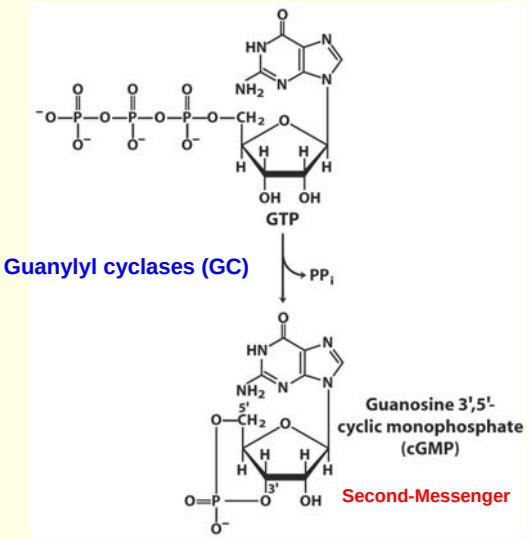
Soluble enzyme/ activated by NO

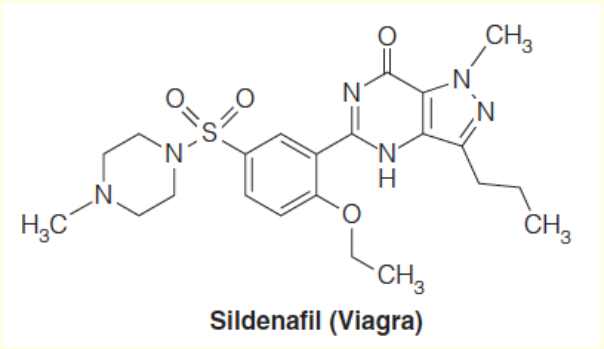
補充 4



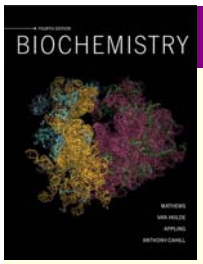
Cyclic GMP

- cGMP /secondary messenger
- cGMP specific ***phosphodiesterase*** (cGMP PED) converts cGMP to the *inactive form 5'-GMP*
- cGMP-dependent protein kinase/ protein kinase G/PKG
- Phosphorylate Ser and Tyr residues in target proteins



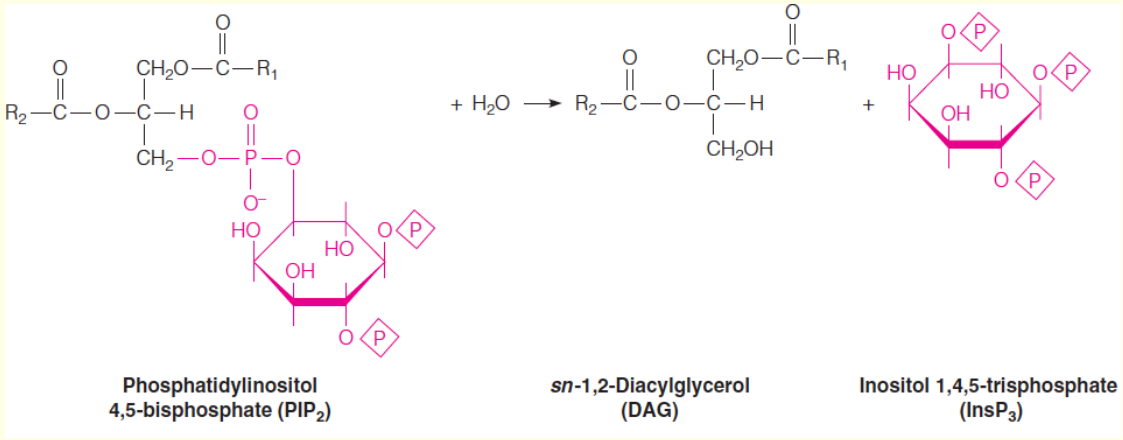


Inhibitor of one of isoform of cGMP PED ⟶ cGMP ↑↑

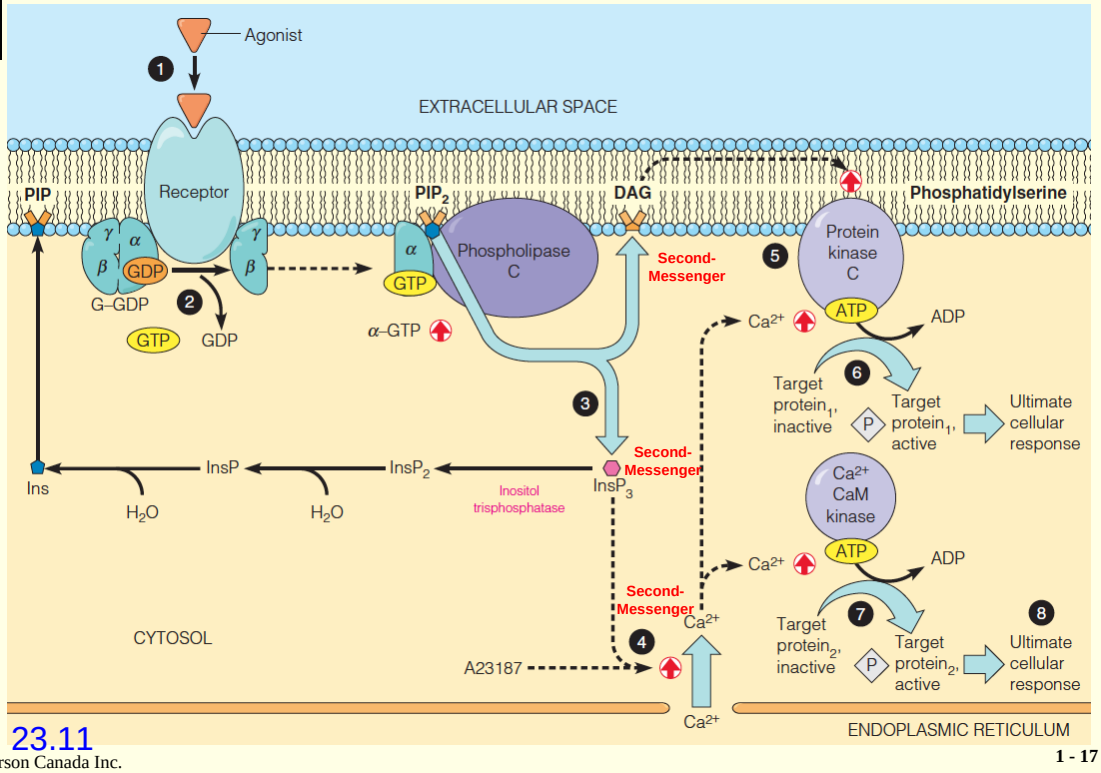


Role of Phosphoinositide in Signal Transduction

- **Phosphatidylinositol 4,5-bisphosphate (PIP_2)** is a membrane-associated storage form for two second messengers - ***sn-1,2-diacylglycerol*** (**DAG**) and **inositol 1,4,5-trisphosphate (**$insIP_3$**)**
- The second-messenger role of inositol trisphosphate is to bind to and open calcium channels in the endoplasmic reticulum (ER), thereby releasing calcium from its intracellular stores in the ER.



Signal transduction pathways involving phosphoinositide turnover

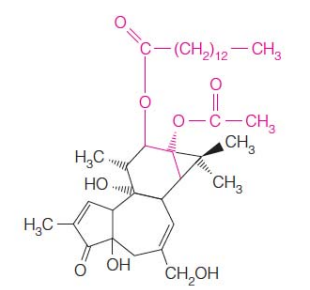


23.11

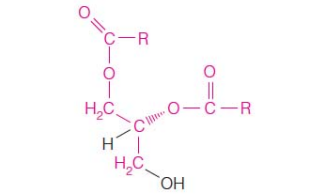
TABLE 23.2 Some cellular processes controlled by the phosphoinositide second-messenger system

Extracellular Signal	Target Tissue	Cellular Response
Acetylcholine	Pancreas	Amylase secretion
	Pancreas (islet cells)	Insulin release
	Smooth muscle	Contraction
Vasopressin	Liver	Glycogenolysis
Thrombin	Blood platelets	Platelet aggregation
Antigens	Lymphoblasts	DNA synthesis
	Mast cells	Histamine secretion
Growth factors	Fibroblasts	DNA synthesis
Spermatozoa	Eggs (sea urchin)	Fertilization
Light	Photoreceptors (*Limulus*)	Phototransduction
Thyrotropin-releasing hormone	Pituitary anterior lobe	Prolactin secretion

The role of phosphoinositide in in the control of cellular growth



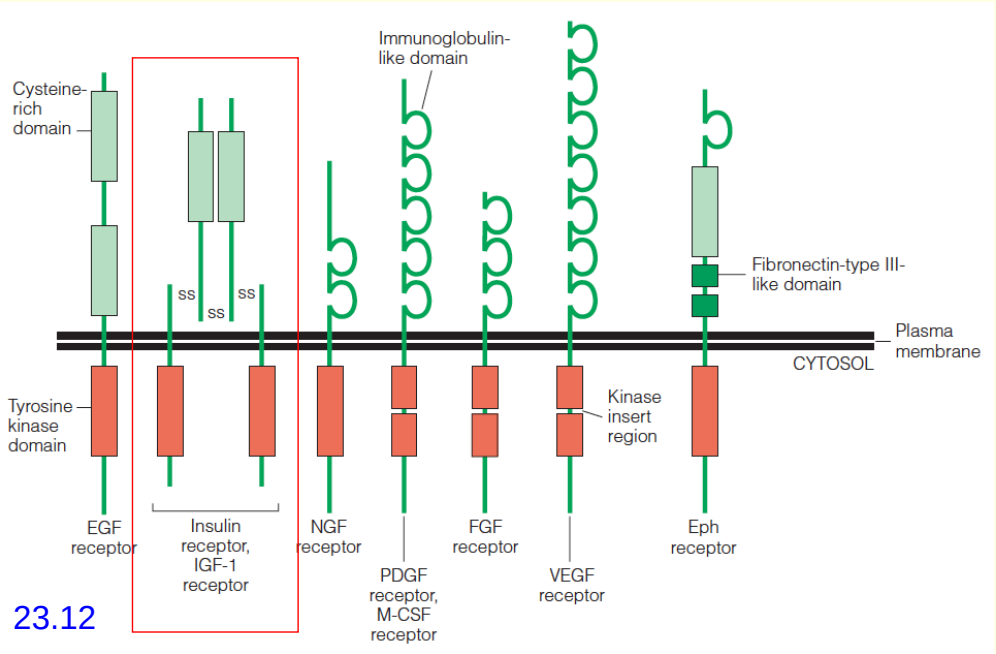
A phorbol ester, 1-*O*-tetradecanoylphorbol-13-acetate



sn-1,2-Diacylglycerol (DAG)

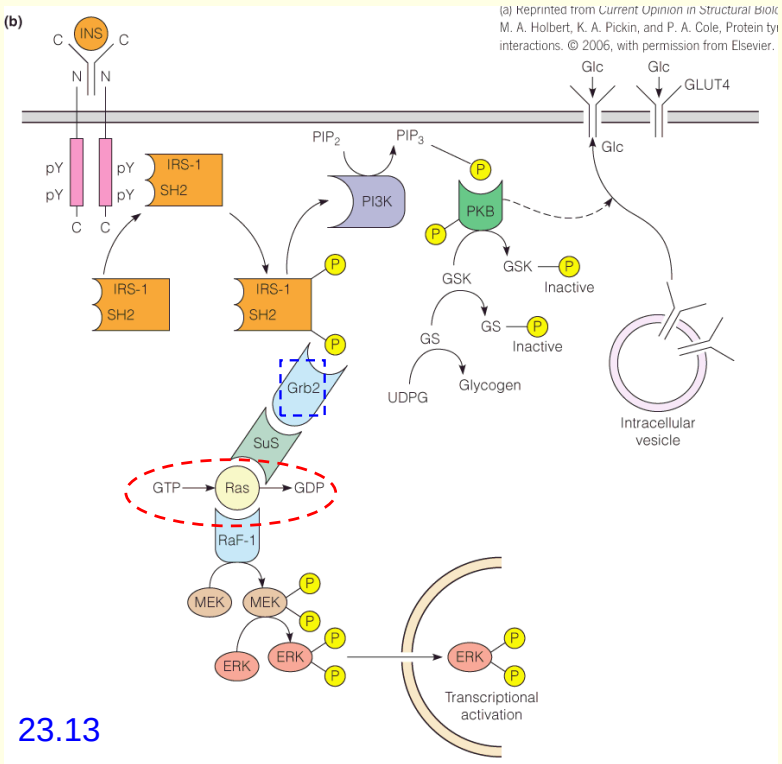
- The phosphoinositide system has a role not only in metabolic regulation but also in the control of cellular growth.
- ***phorbol esters***, natural products part of whose structure resembles that of DAG (shown in red).
- ***tumor promoters*.**
- Some phorbol esters have been found to activate protein kinase C.
- ***platelet-derived growth factor*** (**PDGF**), are known to interact with cell surface receptors to stimulate the hydrolysis of phosphatidylinositol.

Receptor Tyrosine Kinases



The insulin receptor and its structural relationship to other transmembrane receptors with protein tyrosine kinase activity.

Signaling pathways involving the insulin receptor



23.13

Some *binding modules* of signaling proteins
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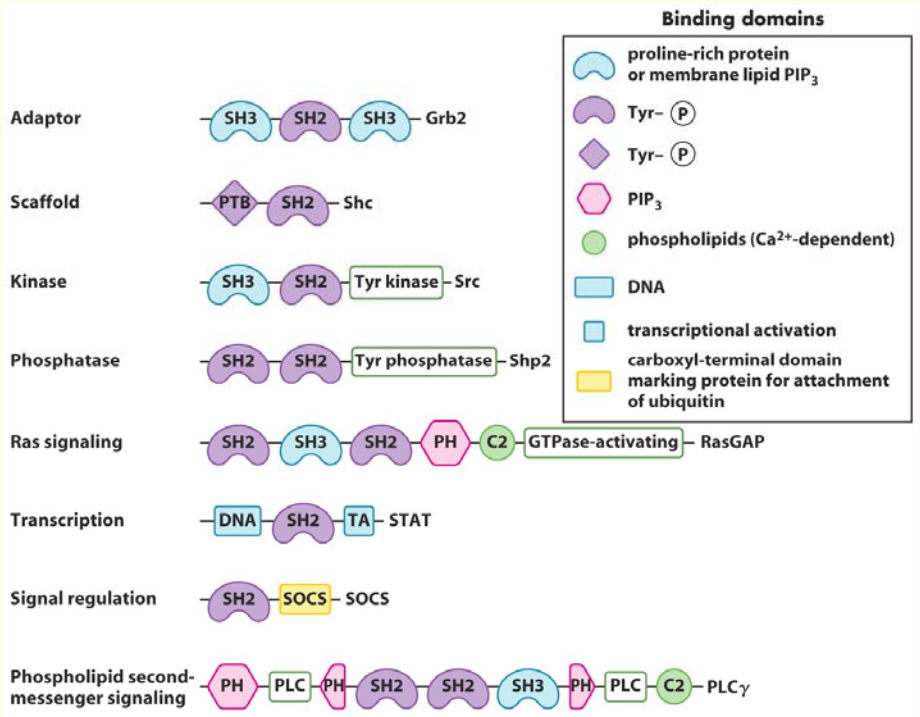
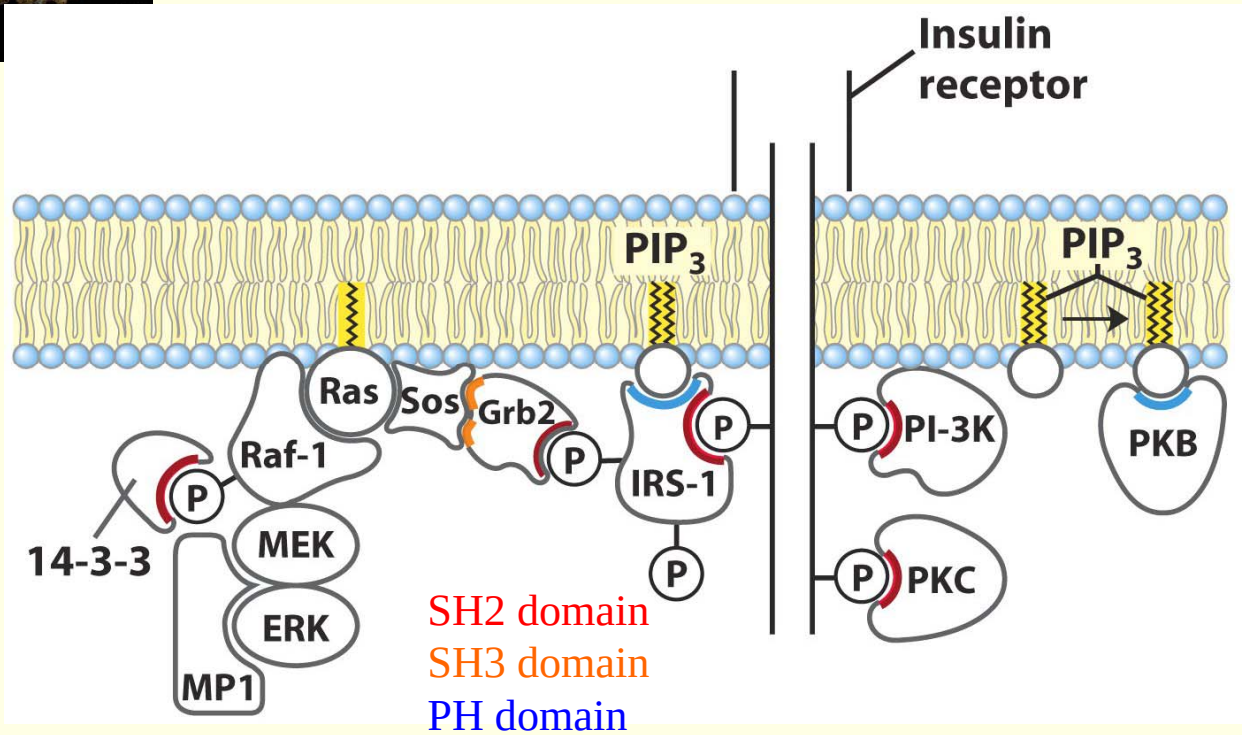


補充 5

Insulin-induced formation of supramolecular signaling complexes



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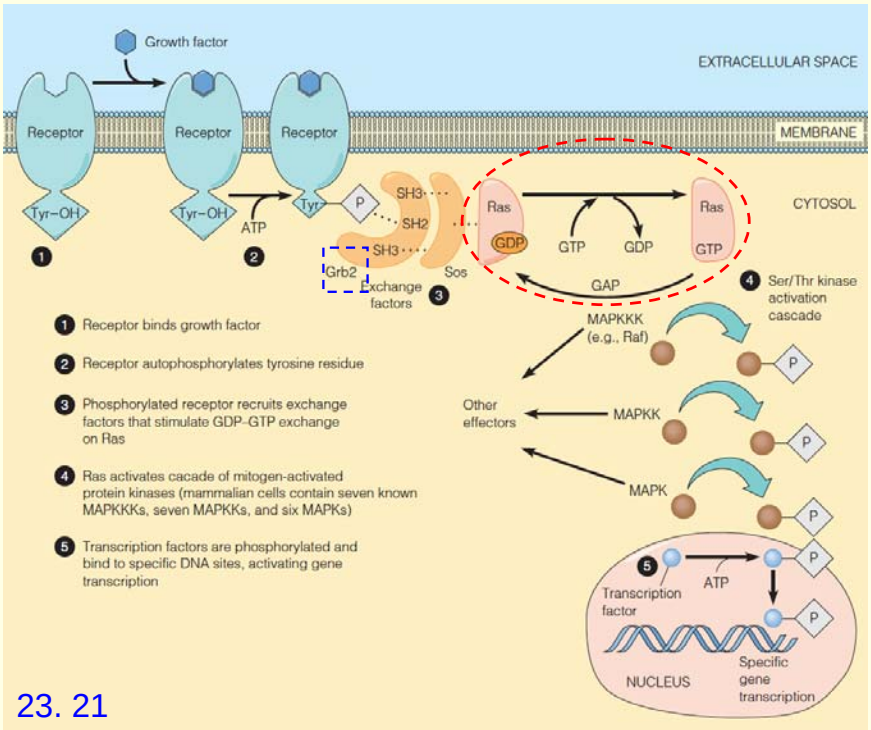
Role of Ras protein in a central growth factor activation pathway



23. 21

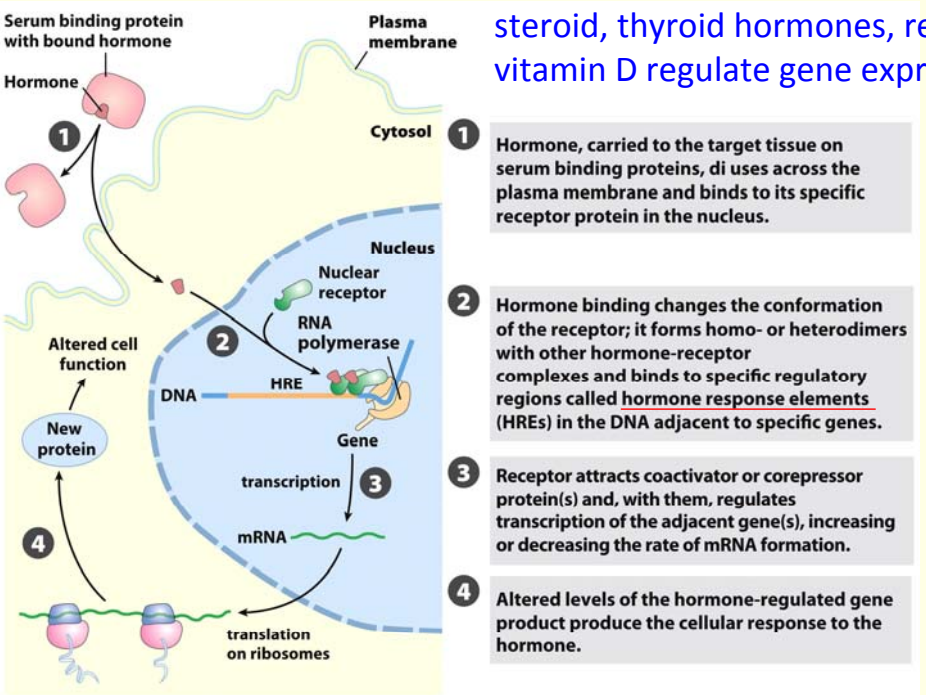
Steroid and Thyroid Hormones: Intracellular Receptors

TABLE 23.3 Target organs for steroid and thyroid hormones and major proteins whose synthesis is affected

Hormone Class	Target Organ	Protein[a]
Glucocorticoids	Liver	Tyrosine aminotransferase
		Tryptophan oxygenase
		α-Fetoprotein (↓)
		Metallothionein
	Liver, retina	Glutamine synthase
	Kidney	Phosphoenol carboxykinase
	Oviduct	Ovalbumin
	Pituitary	Pro-opiomelanocortin
Estrogens	Oviduct	Ovalbumin
		Lysozyme
	Liver	Vitellogenin
		Apo-VLDL
Progesterone	Oviduct	Ovalbumin
		Avidin
	Uterus	Uteroglobin
Androgens	Prostate	Aldolase
	Kidney	β-Glucuronidase
	Oviduct	Albumin
1,25-Dihydroxyvitamin D_3	Intestine	Calcium-binding protein
Thyroid hormones	Liver	Carbamoyl phosphate synthetase
		Malic enzyme
	Pituitary	Growth hormone
		Prolactin (↓)
Ecdysone (insects)	Epidermis	Dopa decarboxylase
	Fat body[b]	Vitellogenin

The family of steroid receptors contains a conserved, zinc-containing DNA-binding sequence and a C-terminal hormone-binding domain.

Direct Regulation of Transcription by Hormones



steroid, thyroid hormones, retinoids and vitamin D regulate gene expression

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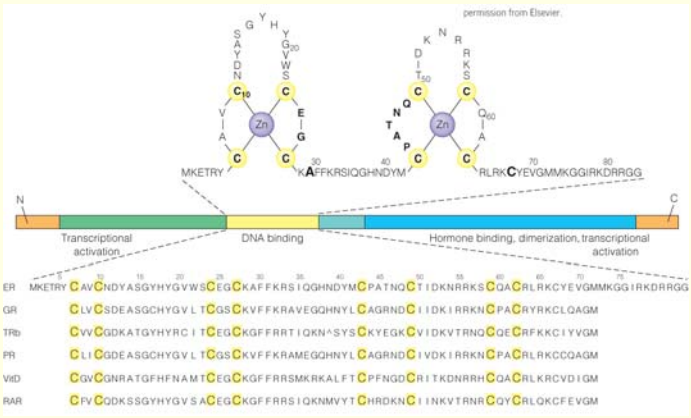
The conserved DNA-binding domain in steroid receptors

•In the center are structural domains within steroid receptors, illustrated for the estrogen receptor.

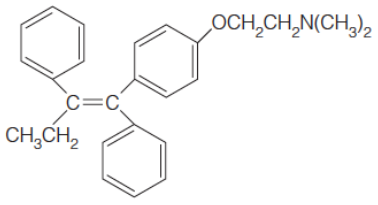
•Above is the DNA-binding domain of the estrogen receptor, showing conserved cysteine residues that contact the bound zinc ions (a zinc finger DNA-binding motif.

•At the bottom are the DNA-binding domain sequences of related human receptors, with the conserved cysteine residues highlighted.

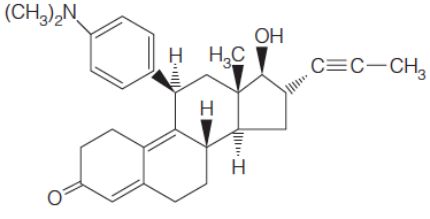


23.14

Steroid hormone receptors are target sites for several important drugs



Tamoxifen



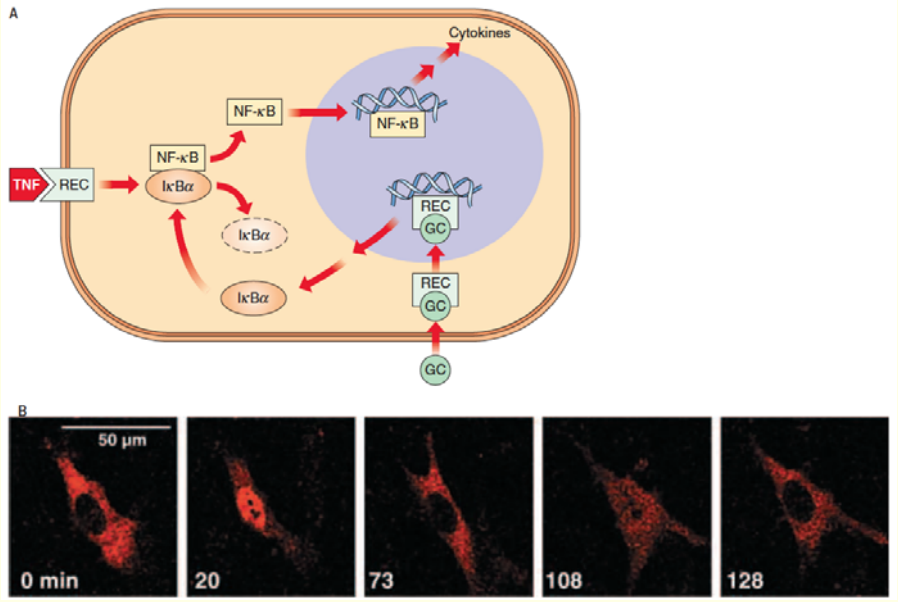
RU486

- ***Tamoxifen*** **(**太莫西芬) binds to estrogen receptors but does not activate estrogen-responsive genes.
- The growth of some breast tumor cells is activated by estrogen. Tamoxifen treatment of patients with such tumors after surgery or chemotherapy often antagonizes estrogen binding in residual tumor cells and retards their growth.
- **RU486**, binds to progesterone receptors and blocks the events essential to implantation of a fertilized ovum in the uterus. Hence, RU486 is an effective contraceptive agent, even when taken after intercourse.

Action of glucocorticoids (GCs, 糖皮質激素) in suppressing immune and inflammatory reactions mediated by cytokines

A. Action of glucocorticoids in counteracting NF-κB translocation to the nucleus.

B. Oscillatory (變動的) nature of the response to TNF signaling.



23.16

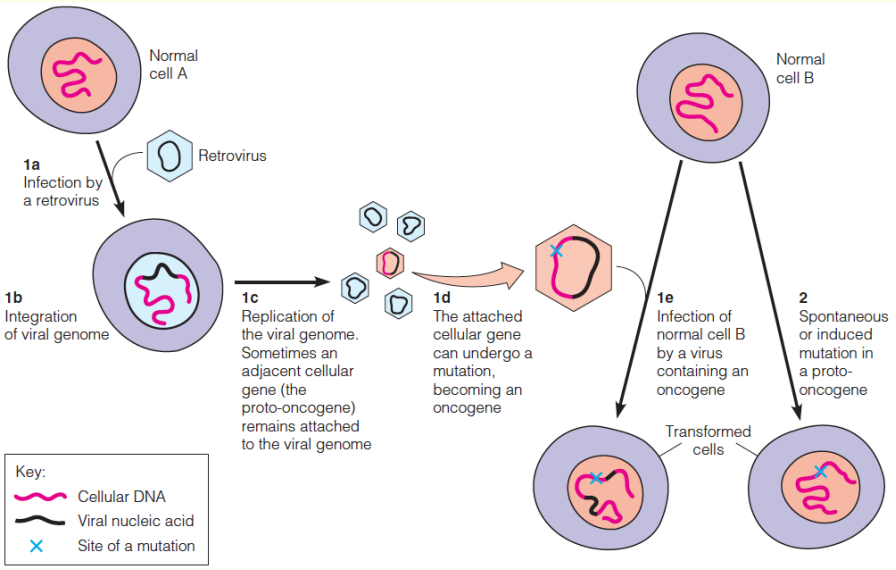
Pathways by which proto-oncogenes can become oncogenes

•A proto-oncogene is a normal cellular gene that can be converted to an oncogene and cause transformation to a cancer cell.

•This process can occur in two ways:

(1) Infection by a virus.

(2) Mutation of the cellular proto-oncogene.



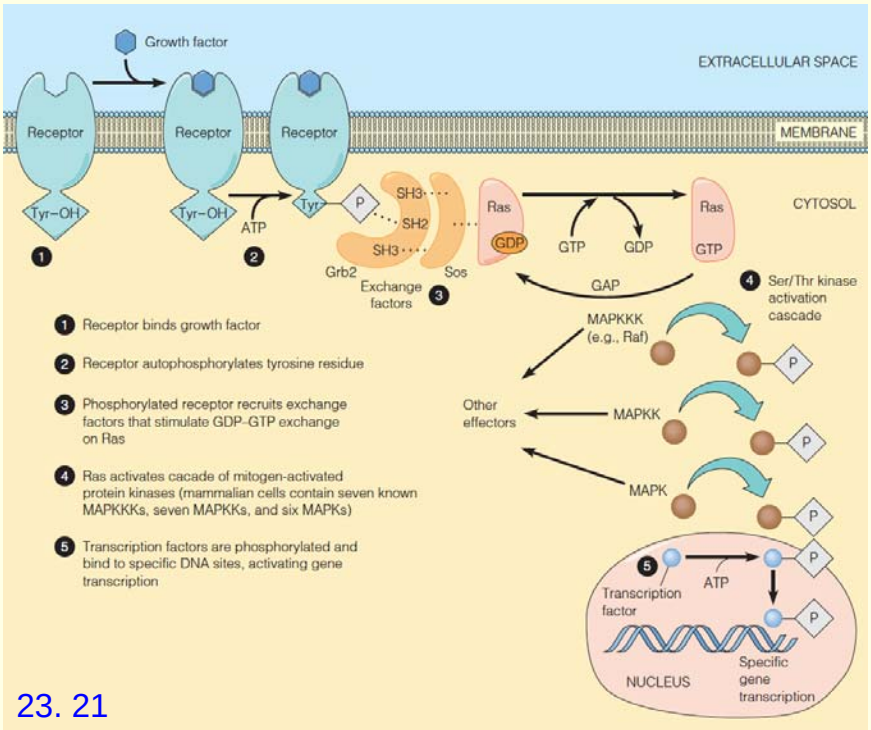
23.17

Signal Transduction and Oncogenes

TABLE 23.4 Oncogene products as elements of signal transduction pathways

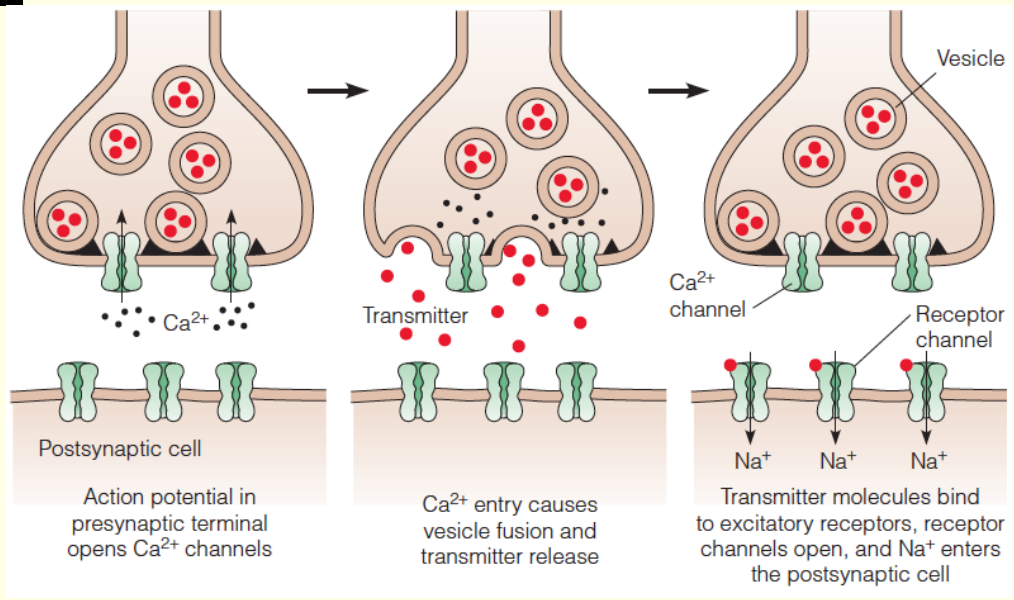
Signal Transduction Element	Oncogene	Isolated from	Gene Product
Growth factors	*sis*	Retrovirus	Platelet-derived growth factor
Growth factor receptors	*erbB, neu*	Retrovirus	Epidermal growth factor receptor
	fms	Retrovirus	Colony-stimulating factor 1 receptor
	trk	Tumor	Nerve growth factor receptor
	ros	Retrovirus	Insulin receptor
	kit	Retrovirus	PDGF receptor
	flg	Retrovirus	Fibroblast growth factor receptor
Intracellular transducers	*src*	Retrovirus	Protein tyrosine kinase
	abl	Retrovirus	Protein tyrosine kinase
	raf	Retrovirus	Protein serine kinase
	gsp	Tumor	G protein α subunit
	ras	Tumor, retrovirus	GTP/GDP-binding protein
Nuclear transcription factors	*jun*	Retrovirus	Transcription factor (AP-1)
	fos	Retrovirus	Transcription factor (AP-1)
	myc	Tumor, retrovirus	Transcription factor
	erbA	Retrovirus	Thyroid receptor

Role of Ras protein in a central growth factor activation pathway



23. 21

Neurotransmission

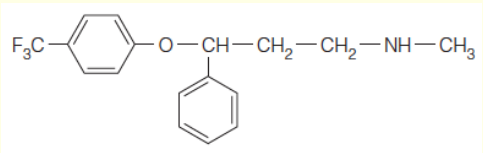


23.23

Transmission of a neural impulse across a synapse, such as a cholinergic synapse

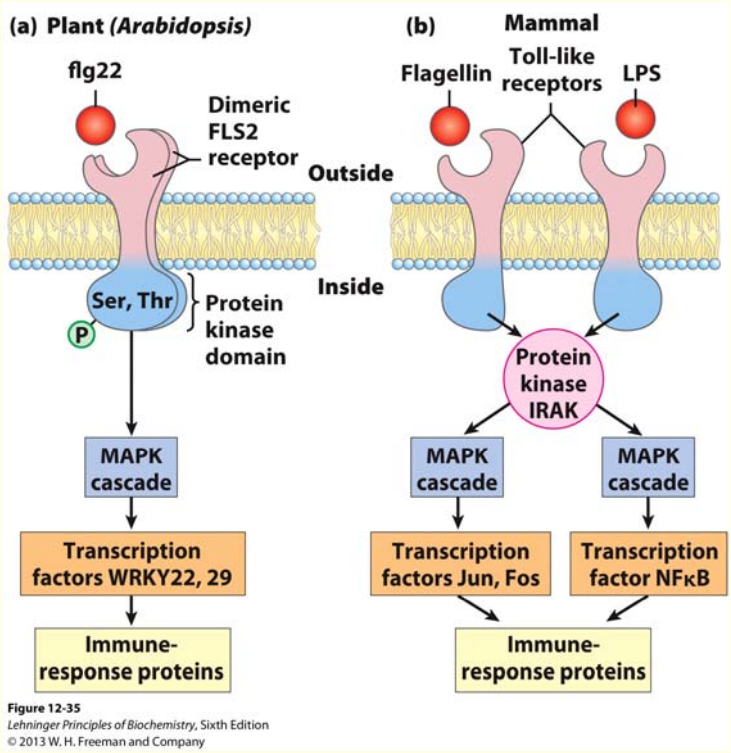
Neurotransmission

- A more recently developed drug, ***fluoxetine*** (**Prozac®**), acts as a selective serotonin reuptake inhibitor (SSRI). 百憂解
- Secreted neurotransmitter has three possible fates:
  - Binding to postsynaptic receptors
  - Catabolism in the cleft
  - Reuptake into the presynaptic cell for re-packaging into storage vesicles.
- Prozac selectively blocks the reuptake of serotonin, thereby increasing the amount that reaches the post-synaptic side and potentiating serotonergic synapses.



Prozac (fluoxetine)

Plants and animals use similar signal transduction pathways



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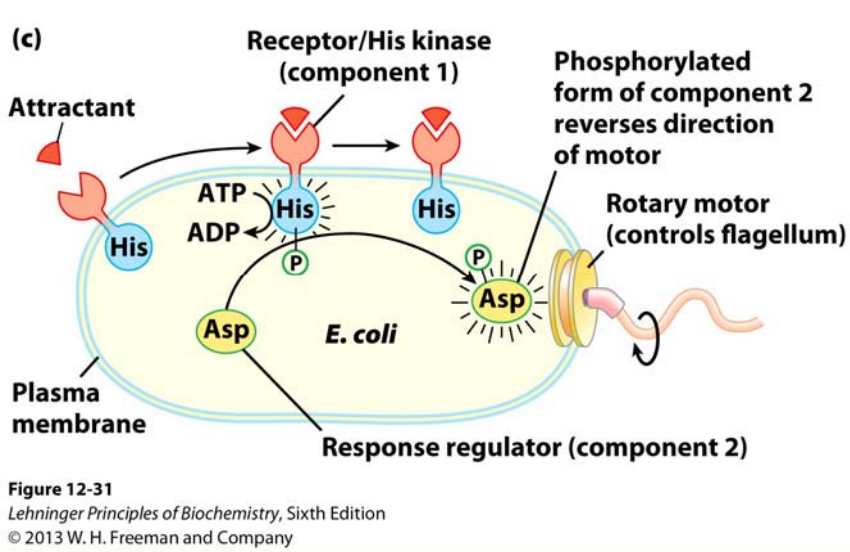
補充 8

Bacterial chemotaxis is controlled by enzyme-coupled receptors

- Two-component signaling mechanism in bacteria chemotaxis
- Receptor His kinase/response regulator



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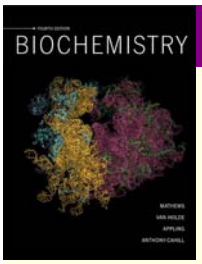

Thank you