Block A: Membrane Biology & Biochemistry

Lipid signaling and sphingolipid function

10.-14.11.2014

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Signal transduction from GPCRs to effector proteins

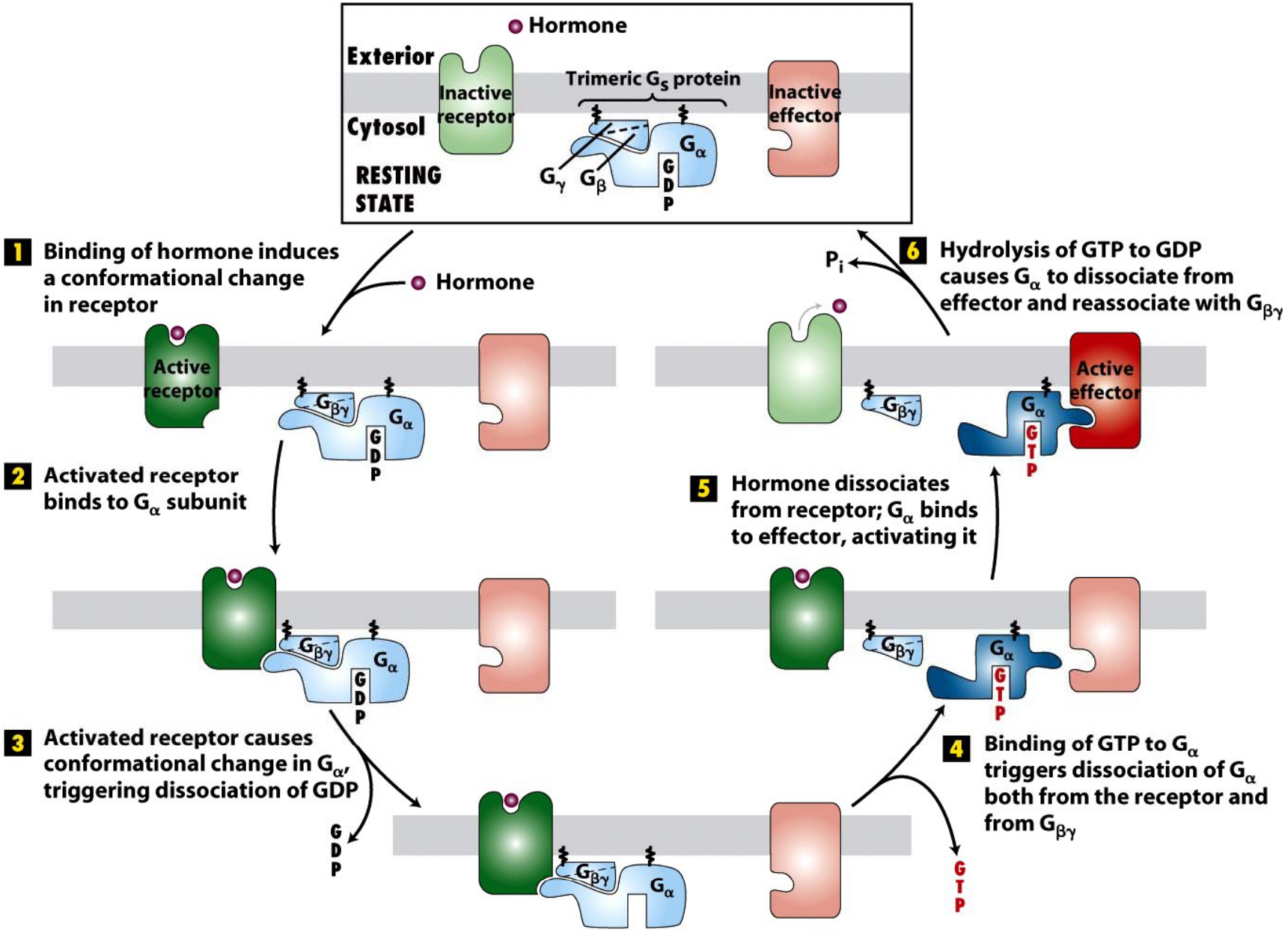
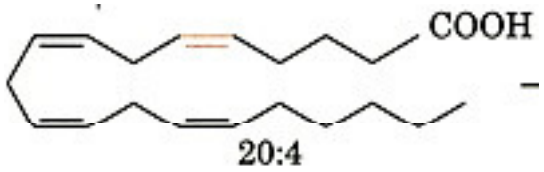


Figure 15-13
Molecular Cell Biology, Sixth Edition

Lodish et al. Molecular Biology of the Cell

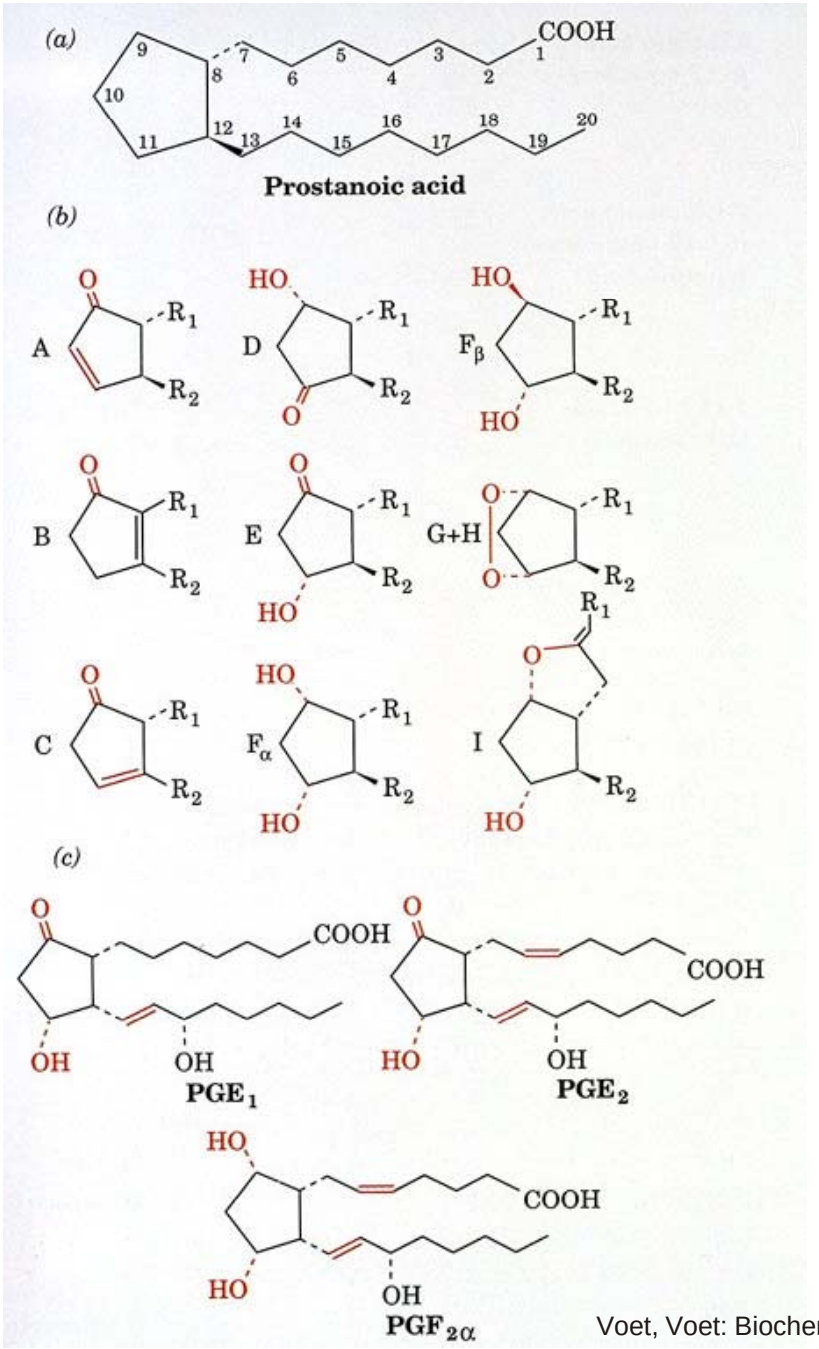


Arachidonic acid

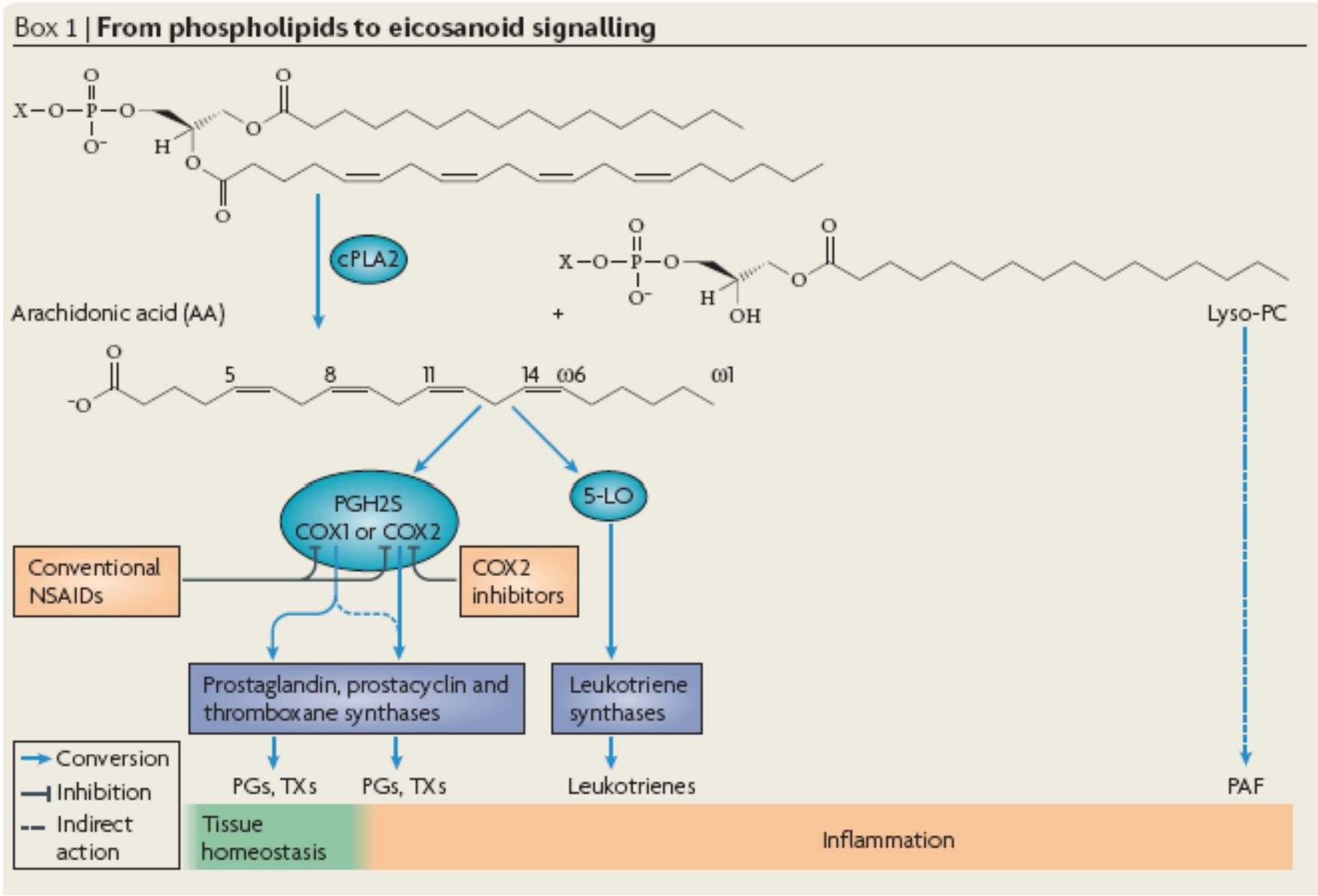
Prostaglandines:
derivatives of the hypothetic prostanoic acid

Ulf von Euler, 1930
(in human seminal fluid)

Regulate physiological processes:
- platelet aggregation
- uterine contractions
- pain, pyrexia (fever)
- inflammation
- secretion of mucins that protect the gastric mucosa from acid and proteases in the stomach

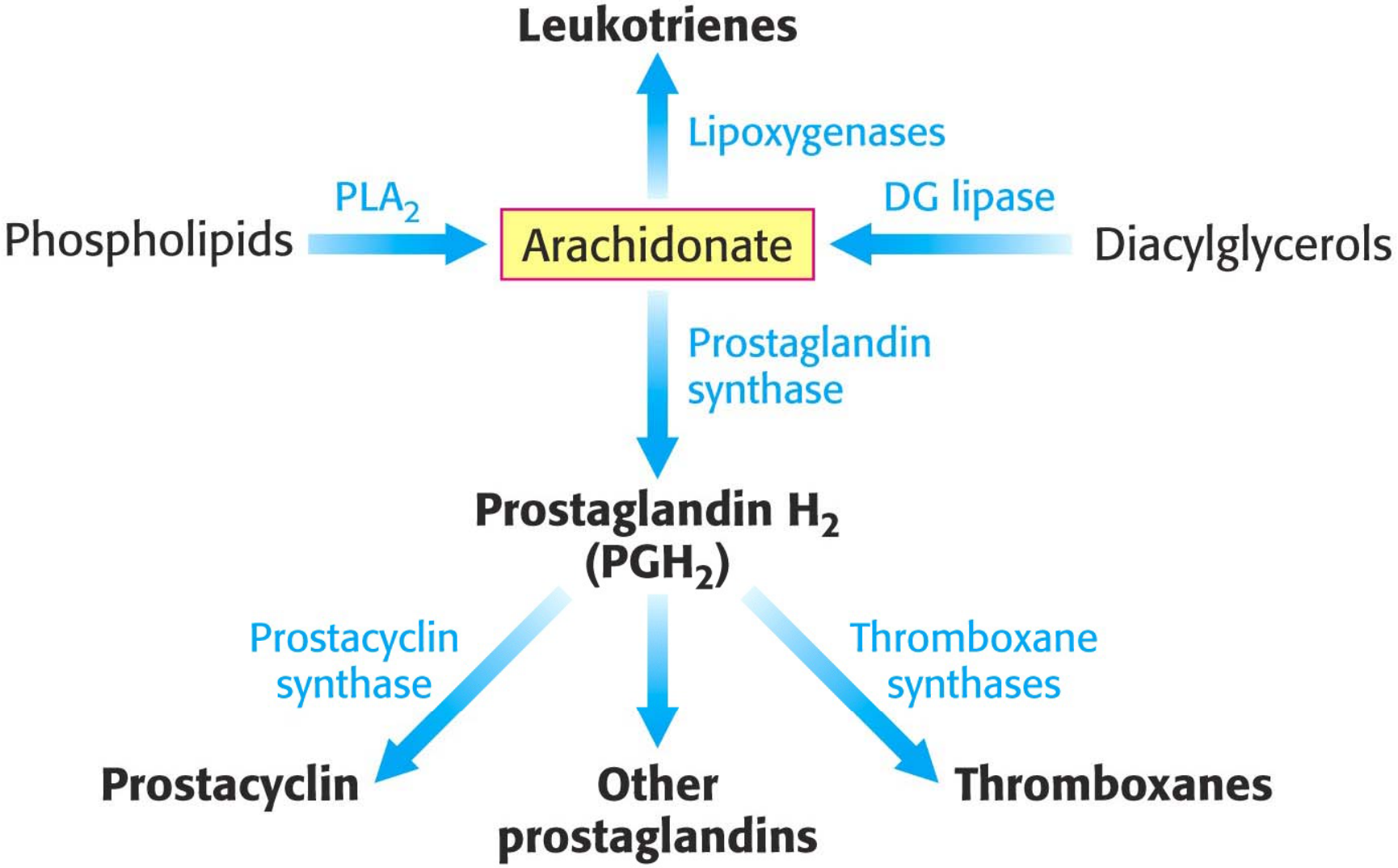


Voet, Voet: Biochemistry



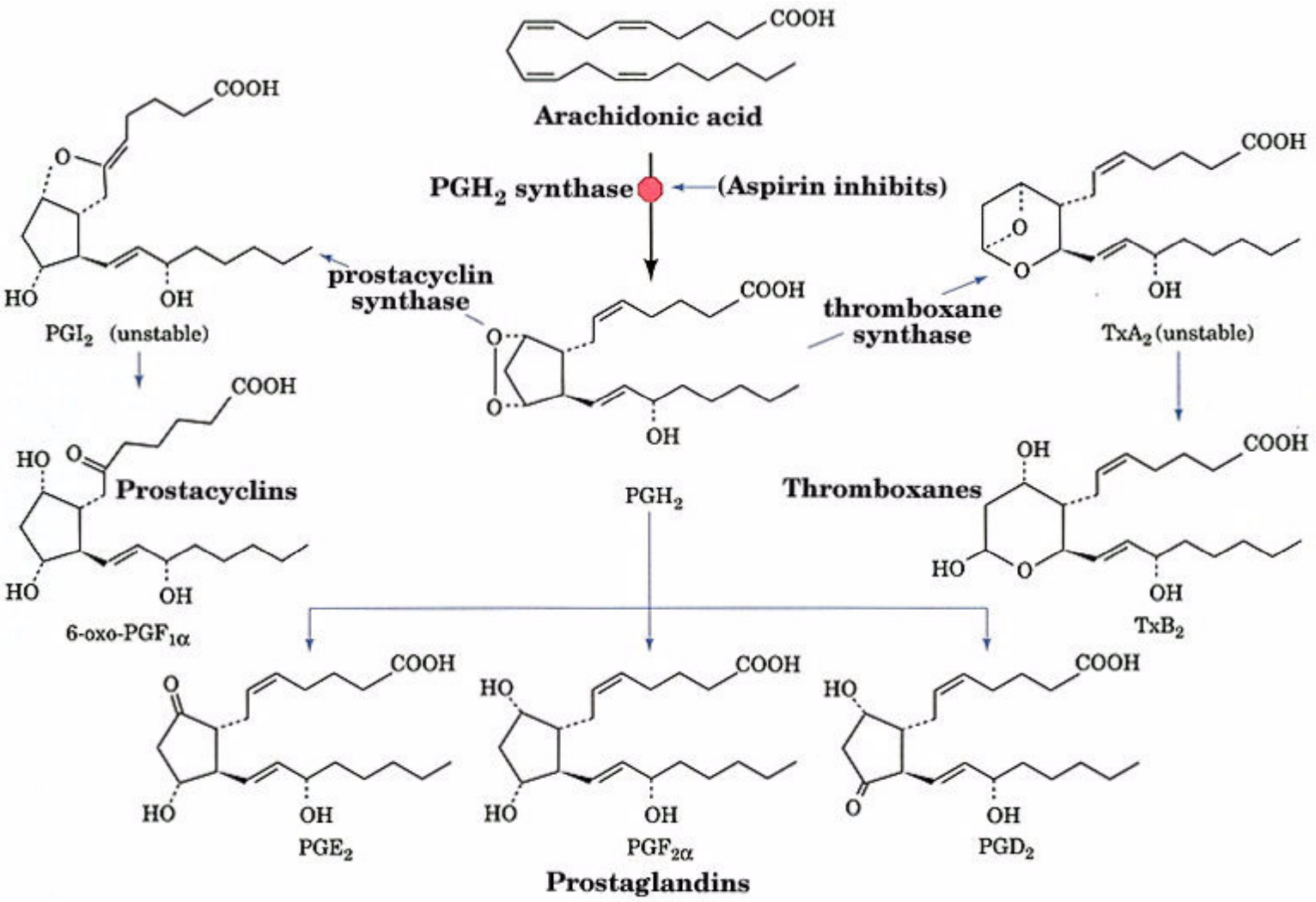
Wymann & Schneiter, Nature, 2008

Metabolism of arachidonic acid



Berg, Tymoczko, Stryer: Biochemistry

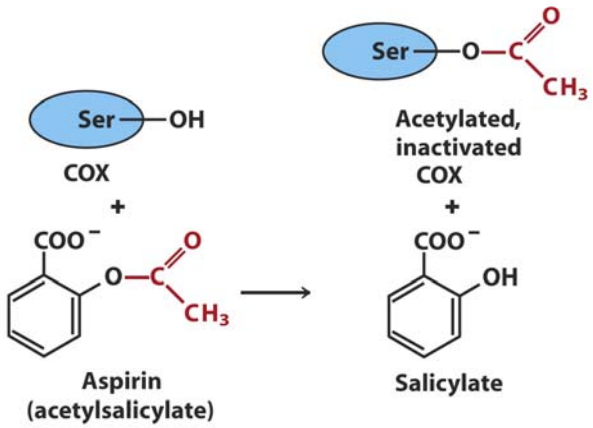
The cyclic fate of arachidonic acid



Voet, Voet: Biochemistry

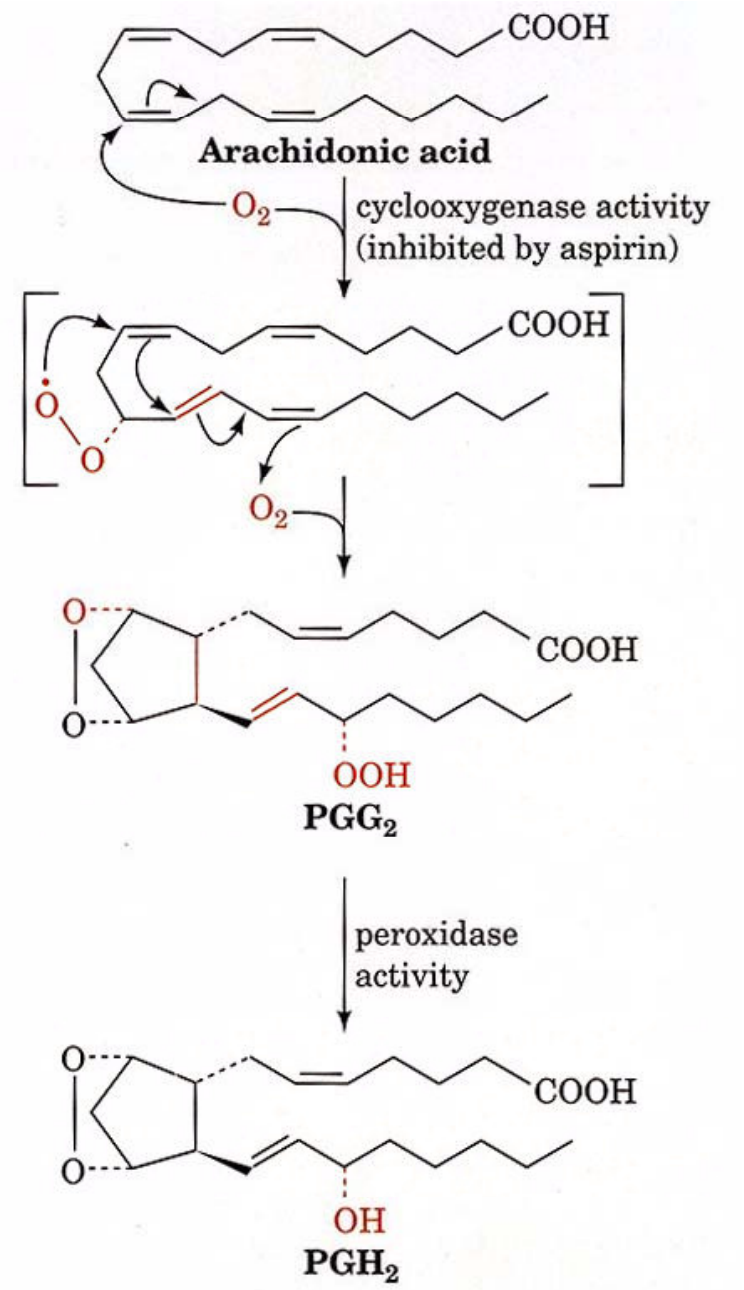
PGH$_2$-Synthase has
2 catalytic activities:

Cyclooxygenase (COX)



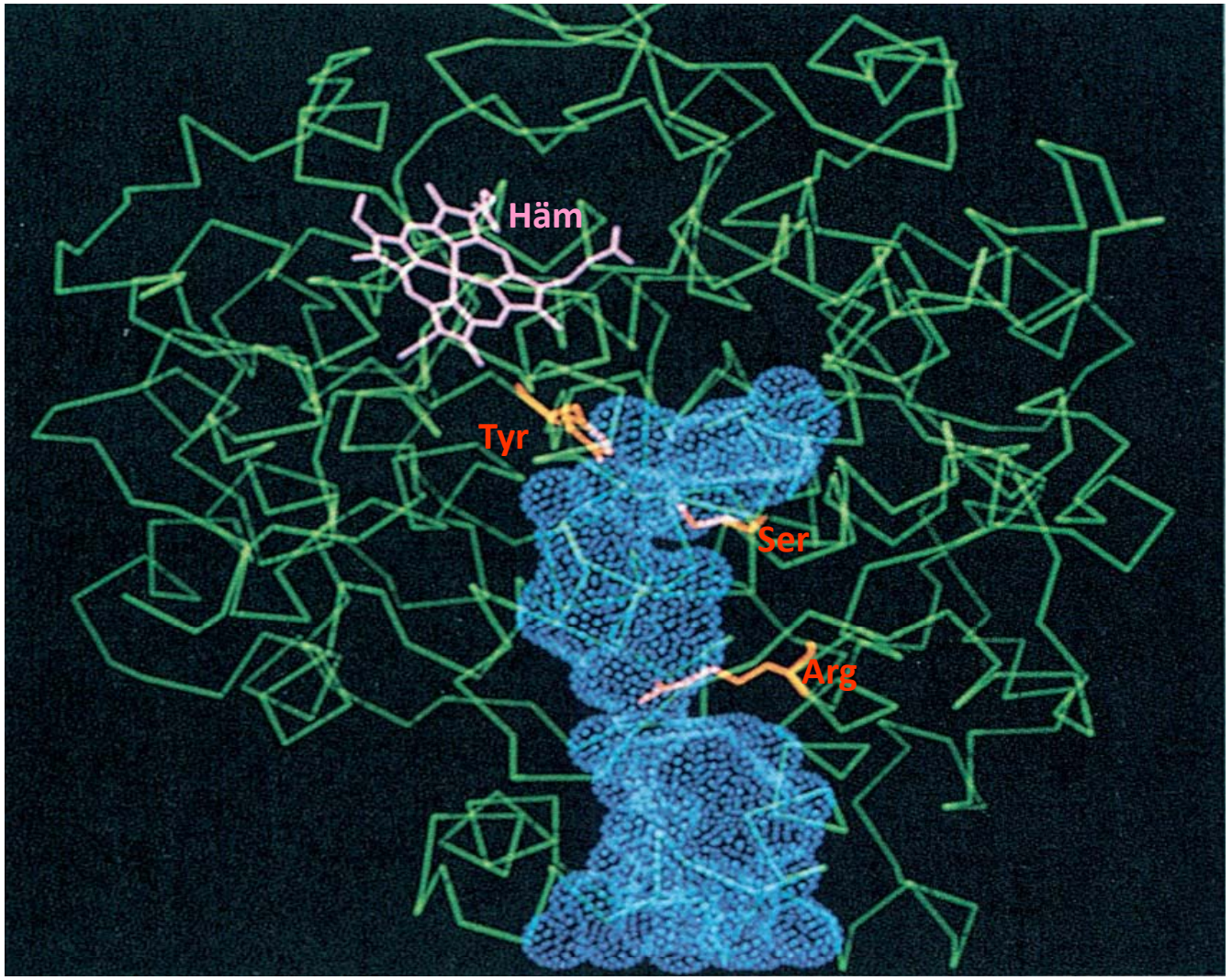
The various effects of Aspirin are based on the inhibition of COX activity

Peroxidase

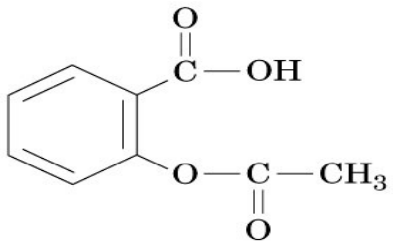


Voet, Voet: Biochemistry

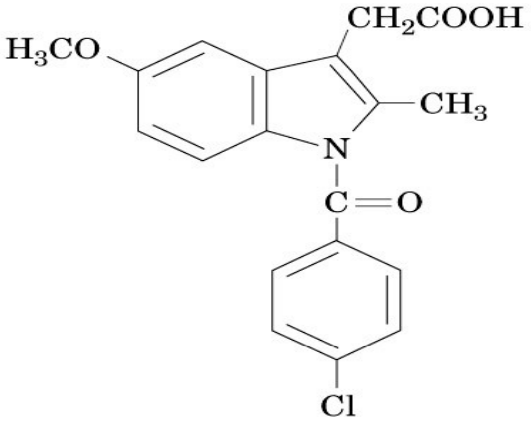
Diagram of one PGHS subunit (*green*).
van der Waals surface of active site channel



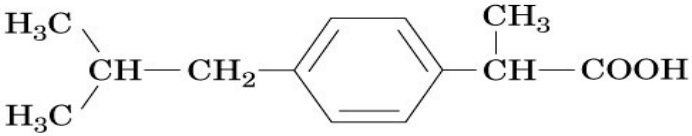
Some nonsteroidal anti-inflammatory drugs (NSAIDs). (side effects due to inhibition of both isoenzymes of COX)



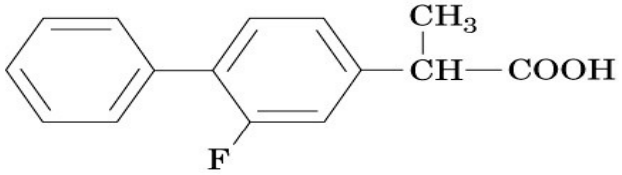
Aspirin
(acetylsalicylic acid)



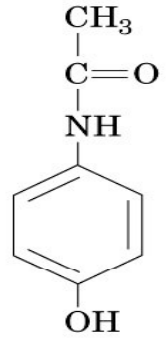
Indomethacin



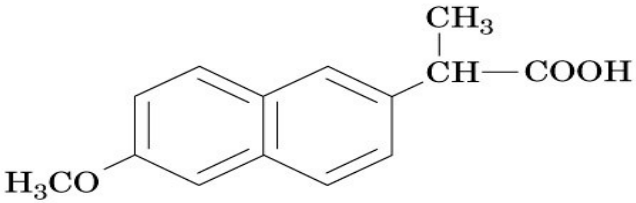
Ibuprofen



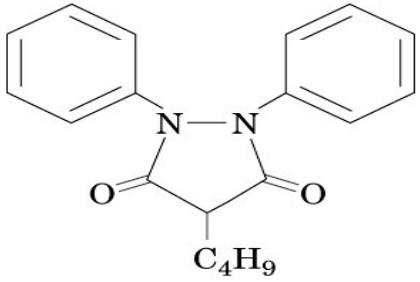
Flurbiprofen



Acetaminophen

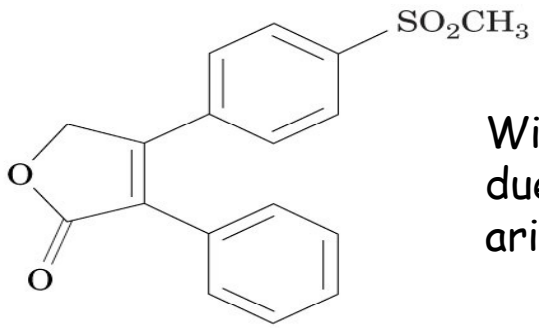


Naproxen



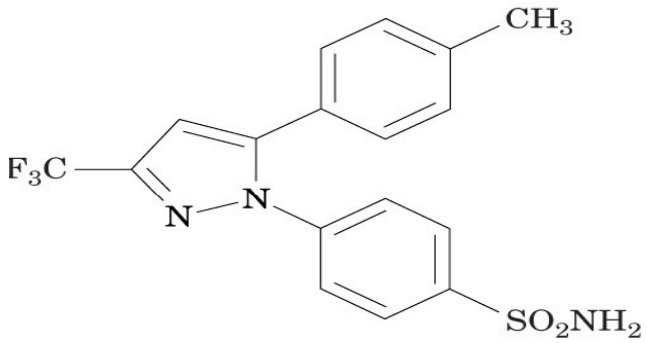
Phenylbutazone

Selective COX-2 inhibitors (coxibs).



Rofecoxib (Vioxx)

Withdrawn from pharmaceutical market due to unanticipated cardiac side effects arising from attenuation of PGI_2 formation!



Celecoxib (Celebrex)

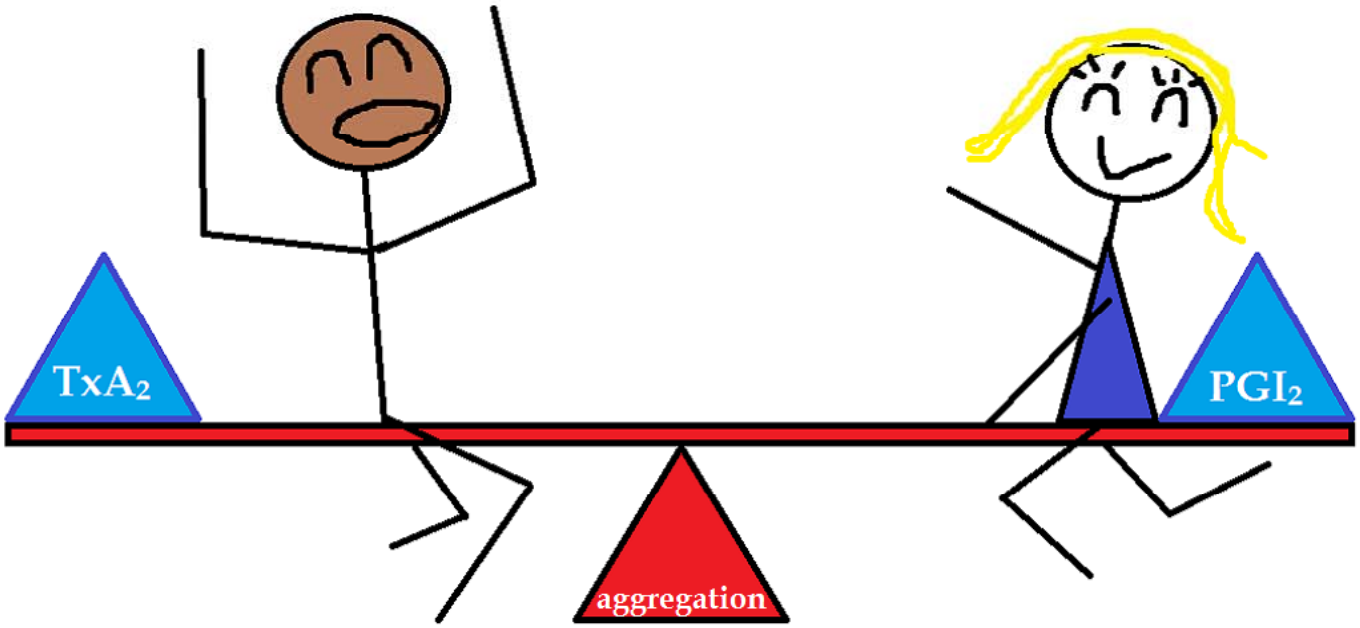
(to large to enter COX-1 active site channel,
that is 20 % smaller in volume than that of COX-2)

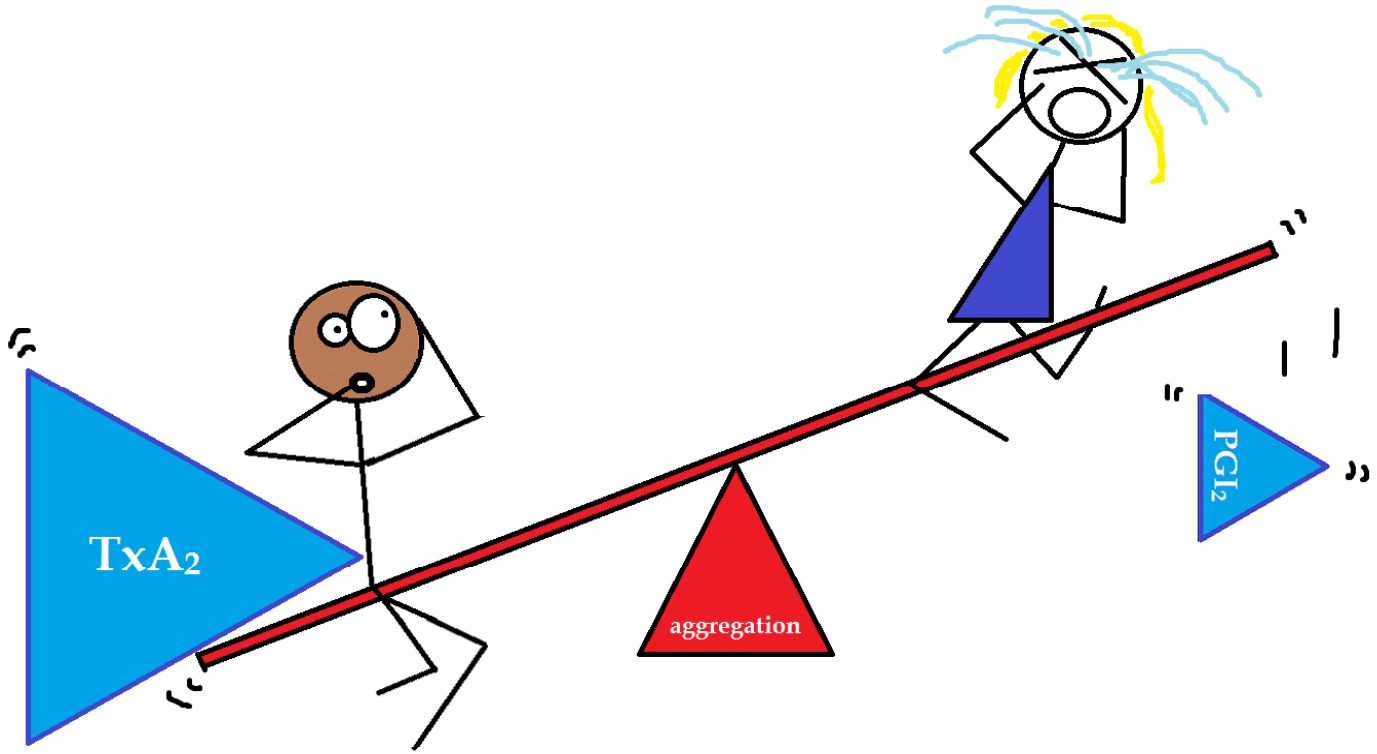
The effects of cyclic endoperoxidases (facilitated by COX1 and COX2)

COX 1	**Stomach (PGE_1)**	Mucous membrane production ↑	Acid production ↓
	Kidney (PGE_2)	Perfusion ↑	Water excretion ↑
	Thrombocytes (TxA_2)	Aggregation ↑	Vasoconstriction

COX 2	**Uterus**	Tone (labor pains, period pain) ↑	
	Vessels (PGI_2)	Vasodilation	Permeability ↑
	Thrombocytes (PGI_2)	Aggregation ↓↑	
	Nociceptors	Sensitivity	
	Fever (PGE_2)	Thermoregulation hypothalamus	

What is the problem of selective COX2 inhibitors? ...





Inhibition of COX2 facilitated prostacyclin biosynthesis and no interference with thromboxan A_2 biosynthesis leads to:

- Higher thrombocyte aggregation → thrombosis
  → myocardial infarction

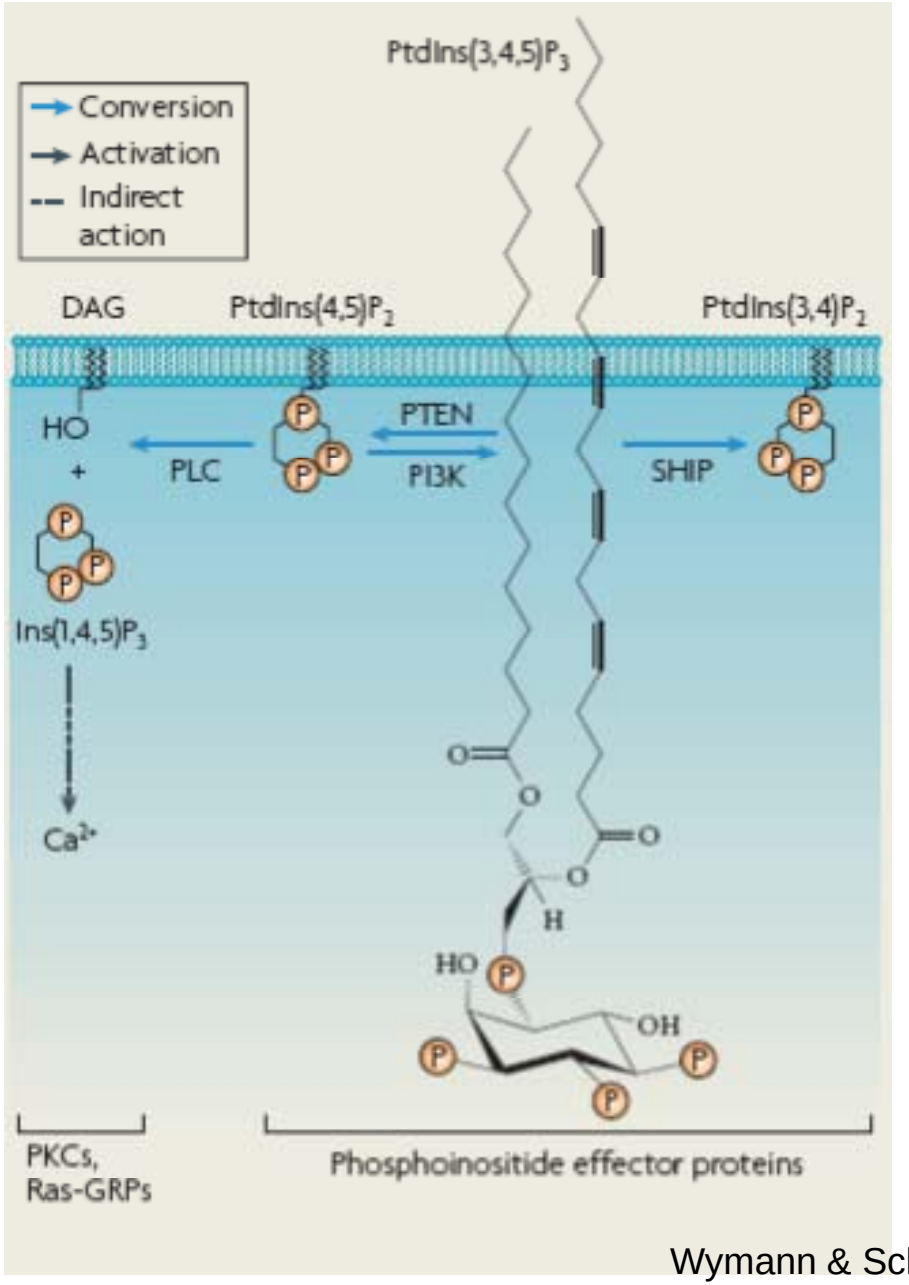
... They kill you. And make cute girls cry.

Phosphoinositides as Signal Transducers

- Phospholipase C: different isoforms are activated by different signals that bind either GPCR or RTK

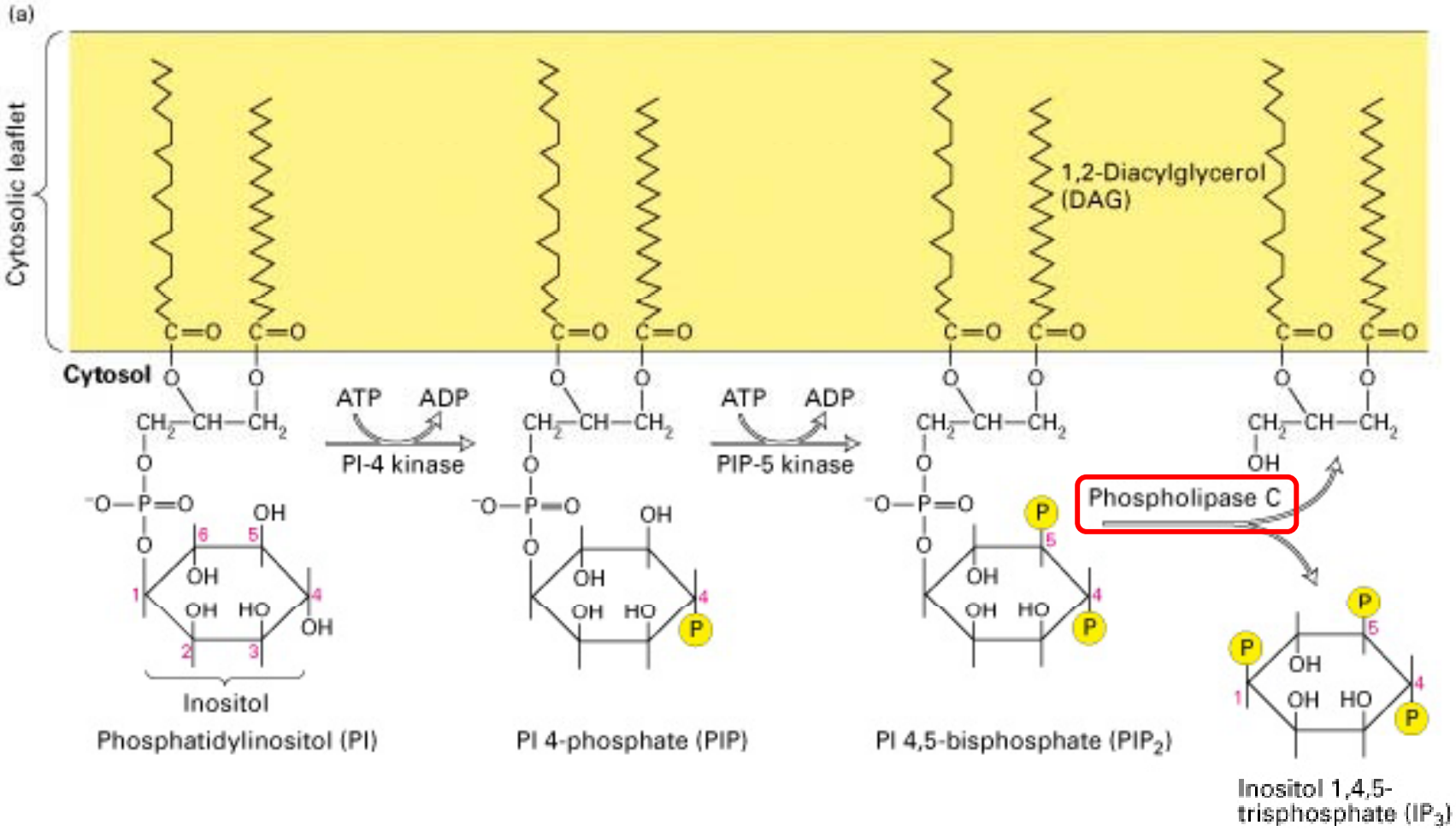
- PI-3 kinase pathway

Intracellular signalling by phosphoinositids



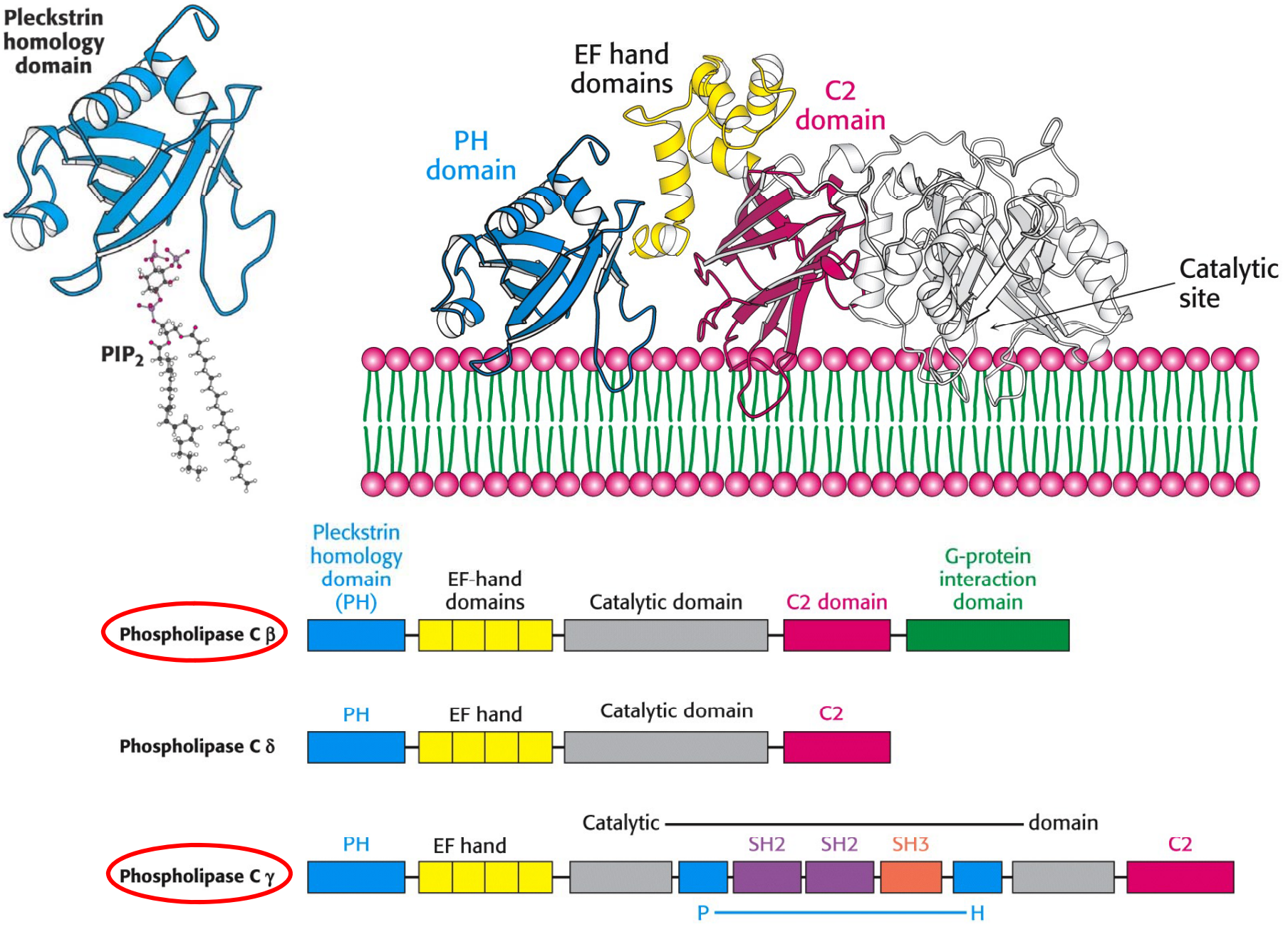
Wymann & Schneiter, Nature, 2008

Modification of a common phospholipid precursor generates several second messengers: synthesis of DAG and IP_3



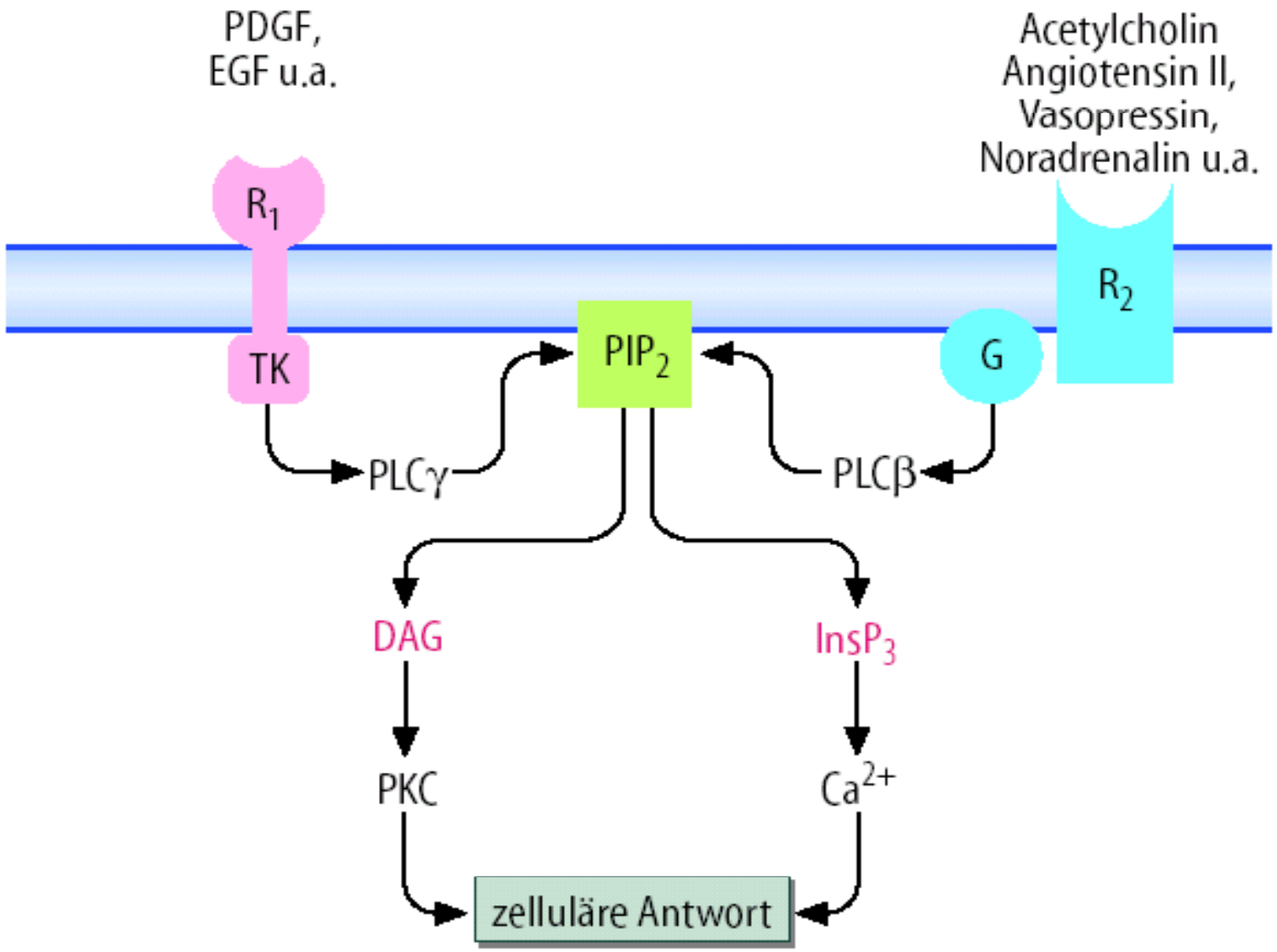
Lodish et al. Molecular Biology of the Cell

Phospholipase C Isoforms



Berg, Tymoczko, Stryer: Biochemistry, 2002

PLC-induced release of Ca^{2+} from the ER is mediated by IP_3



Löffler, Petrides, Biochemie und Pathobiochemie

PLCβ is an effector targeted by GPCRs

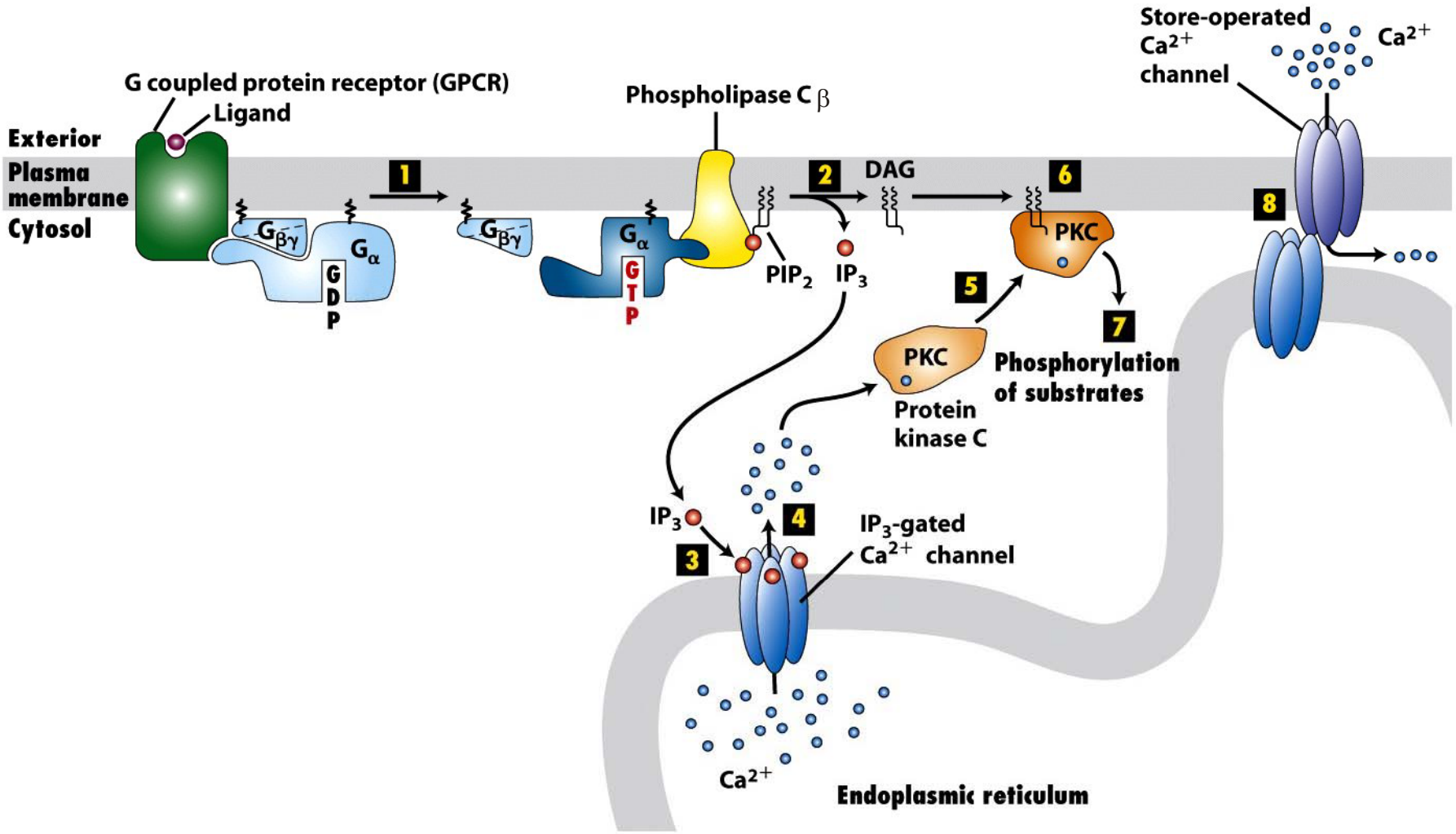
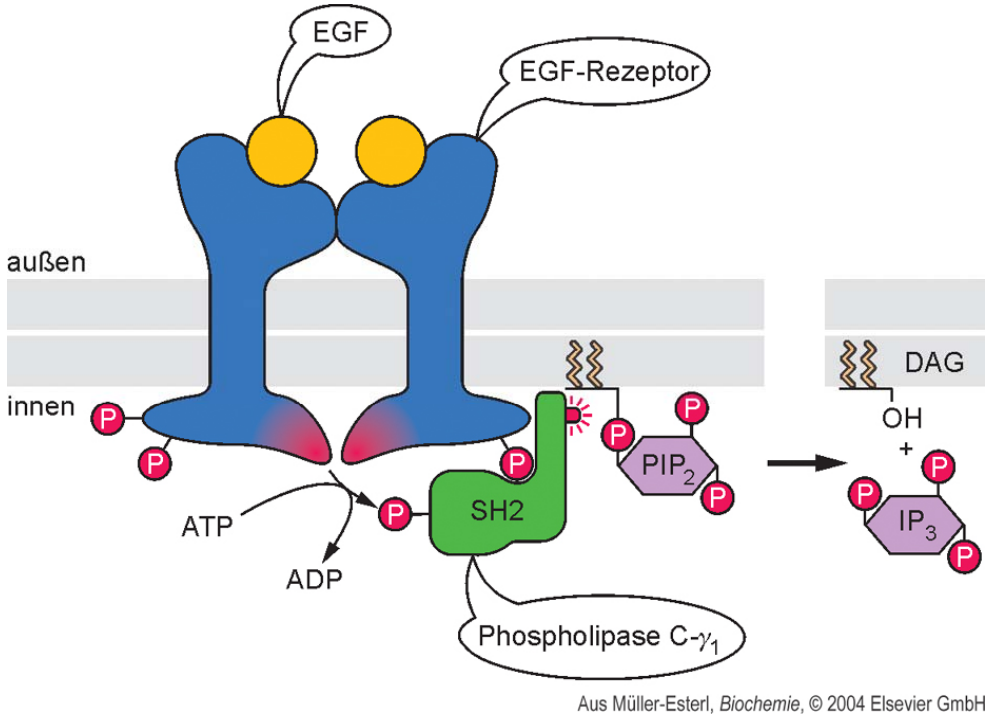


Figure 15-30
Molecular Cell Biology, Sixth Edition

Short term effects on cell metabolism and movement
Long term effects on gene expression

PLCγ_1 is an effector targeted by RTKs



The activated EGF-receptor recruits the cytosolic phospholipase C-γ_1 (substrate PIP_2) via its **SH2-domain** and activates the enzyme by phosphorylation.

Phosphatases terminate this process.

PI 3-phosphates recruit and activate protein kinase B (PKB)

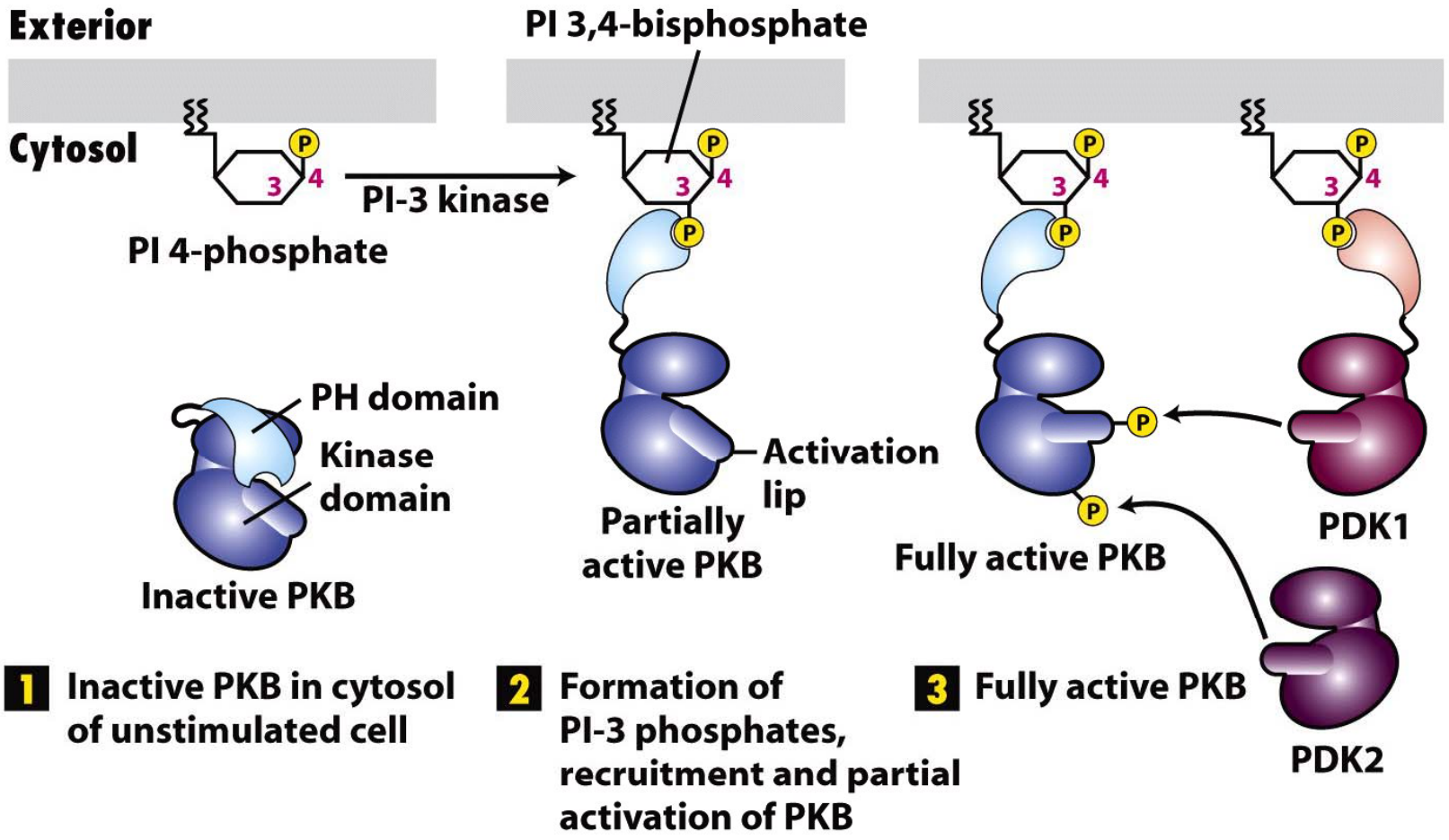


Figure 16-30
Molecular Cell Biology, Sixth Edition

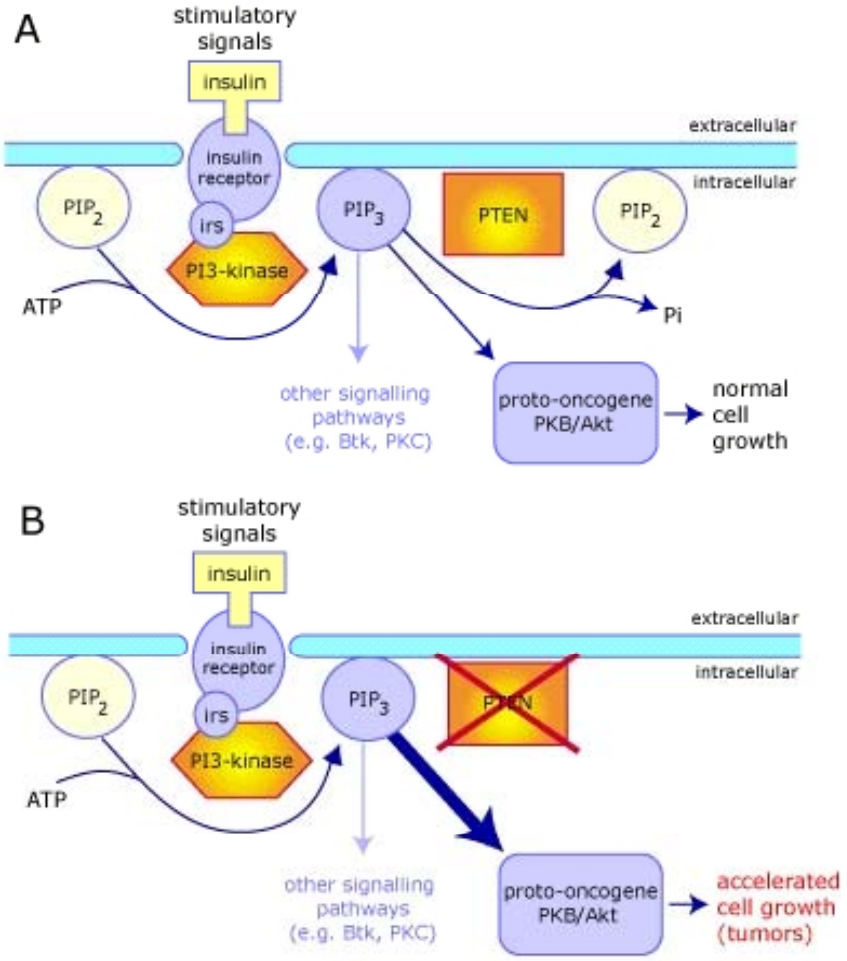
PH: **p**leckstrin **h**omology
PDK: **P**I-**d**ependant **k**inase

PTEN: the first tumour suppressor with phosphatase activity

PTEN phosphatase has a broad specificity but its major function in cells is to reverse the PI-3 kinase catalyzed reaction.

PTEN is deleted or mutated in multiple types of human cancer (glioblastoma, prostate cancer, endometrial tumour).

Overexpression of PTEN promotes apoptosis in cultured mammalian cells.



www.ncbi.nlm.nih.gov/bookshelf/picrender.fcgi...

Mode of action of the nuclear receptor superfamily PPAR

L: fatty acids and derivatives

PPAR: **p**eroxisome **p**roliferator-**a**ctivated **r**eceptor

RXR: retinoid X receptor

PPARα, hepatocytes, turns on genes for FA β-oxidation and ketone body formation during fasting.

.

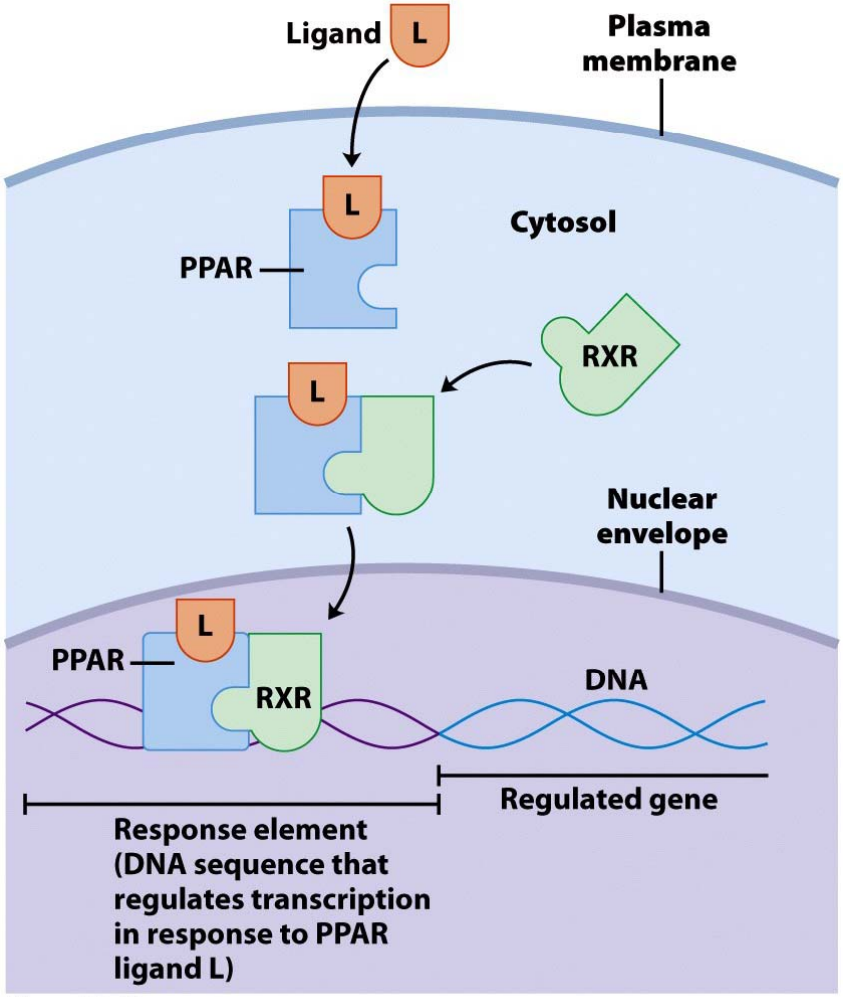


Figure 23-41
Lehninger Principles of Biochemistry, Fifth Edition

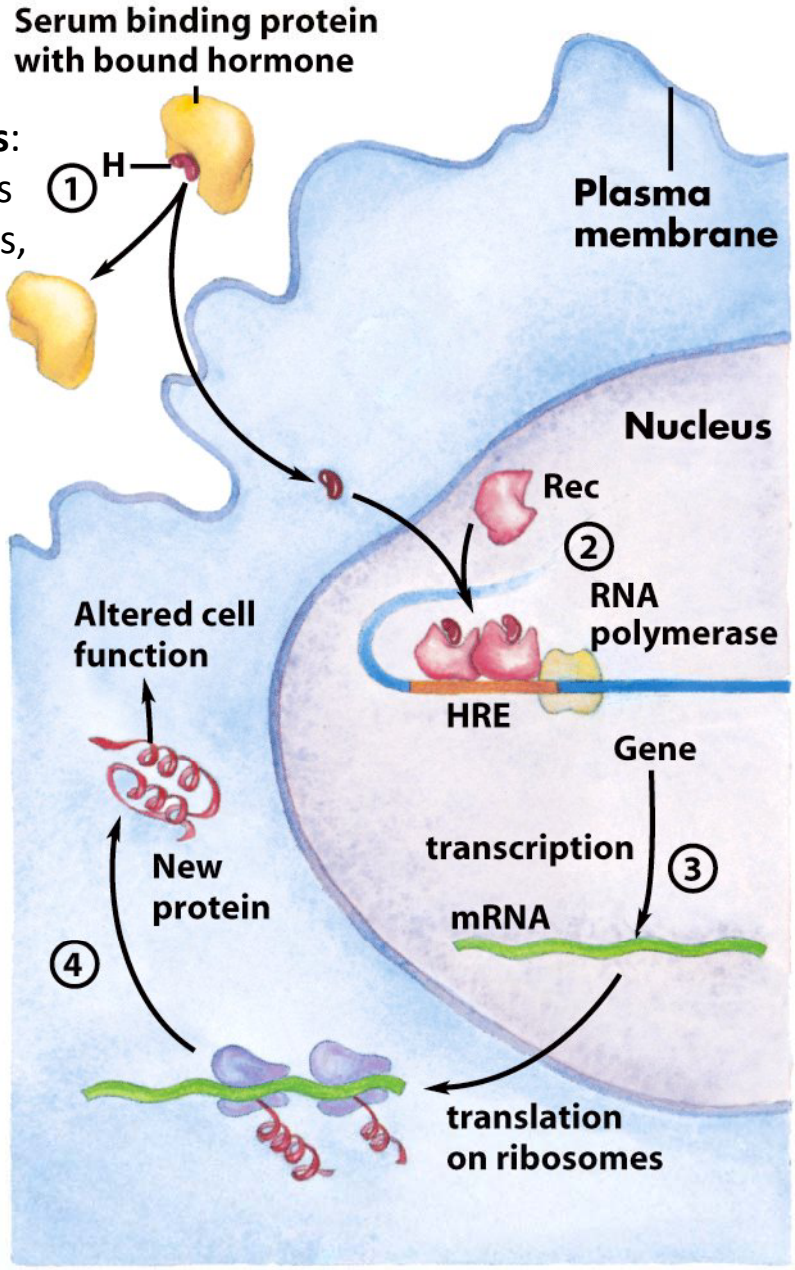
PPARγ, liver & adipose tissue, turns on genes for lipid synthesis, differentiation of fibroblasts into adipocytes.

PPARδ, liver & muscle tissue, turns on genes for β-oxidation and for energy dissipation through uncoupling of mitochondria (prevents obesity).

Diet regulates the expression of genes central to maintaining body mass

General mechanism by which lipophilic compounds regulate gene expression

Lipophilic ligands:
steroid hormones
thyroid hormones,
retinoids (vit. A)
vitamin D



1. Hormone (H), carried to the target tissue on serum binding proteins, diffuses across the plasma membrane and binds to its specific receptor protein (Rec) in the nucleus.
2. Hormone binding changes the conformation of Rec; it forms homo- or heterodimers with other hormone-receptor complexes and binds to specific regulatory regions called hormone response elements (HREs) in the DNA adjacent to specific genes.
3. Binding regulates transcription of the adjacent gene(s), increasing or decreasing the rate of mRNA formation.
4. Altered levels of the hormone-regulated gene product produce the cellular response to the hormone.

Nelson, Cox: Lehninger Biochemistry,