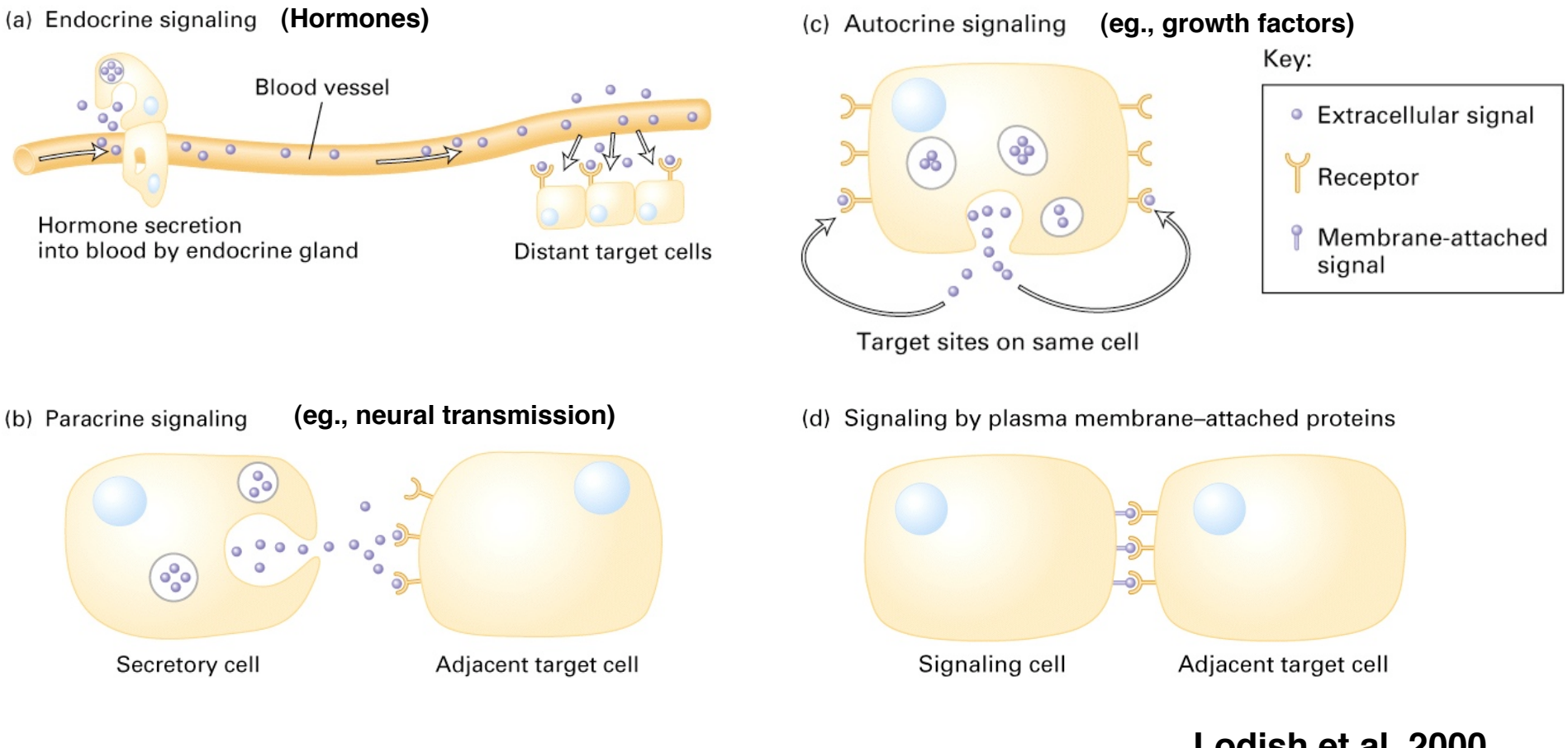
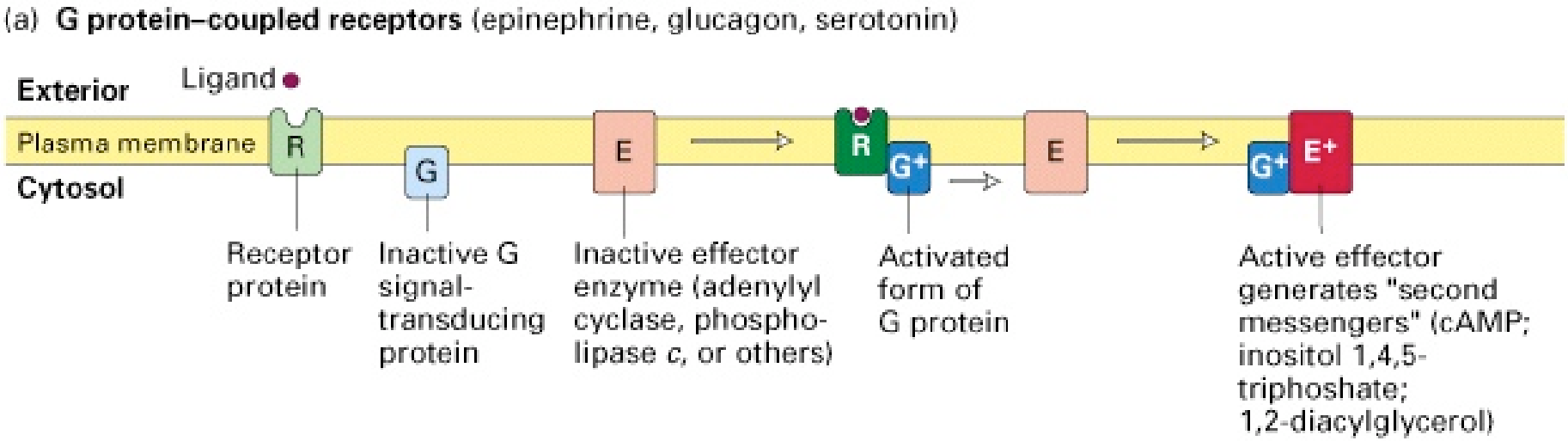
Four types of cell-cell signaling



Lodish et al, 2000

Signal transduction

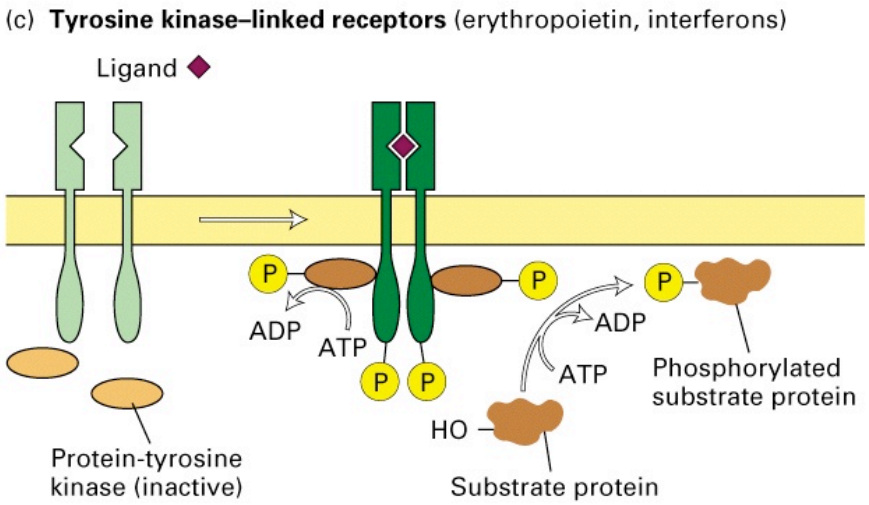
Seven transmembrane receptors
G proteins

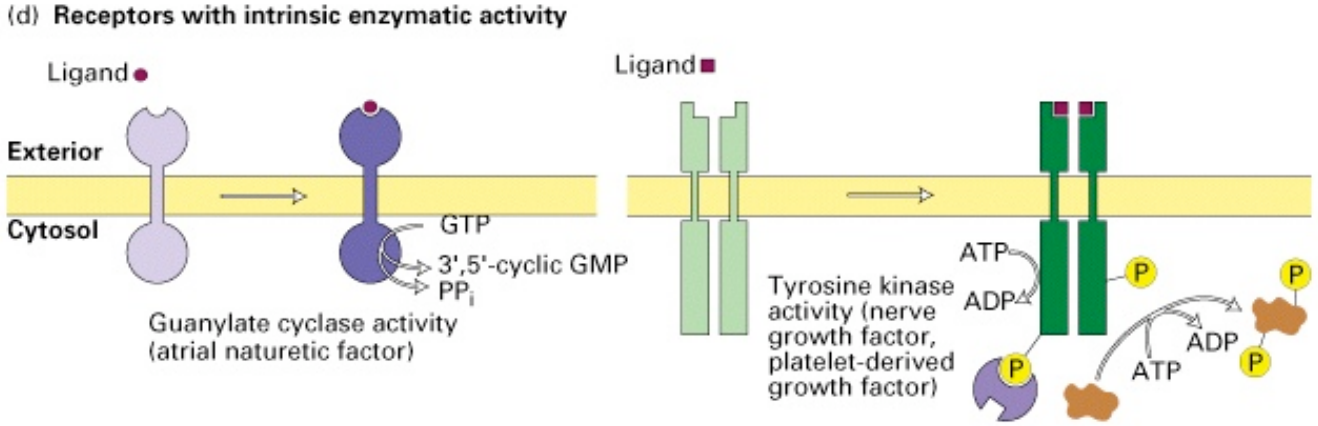


Lodish et al, 2000

Signal transduction

Cytokine receptors-expression cloning
Protein kinases, intracellular signaling-MAPK pathway

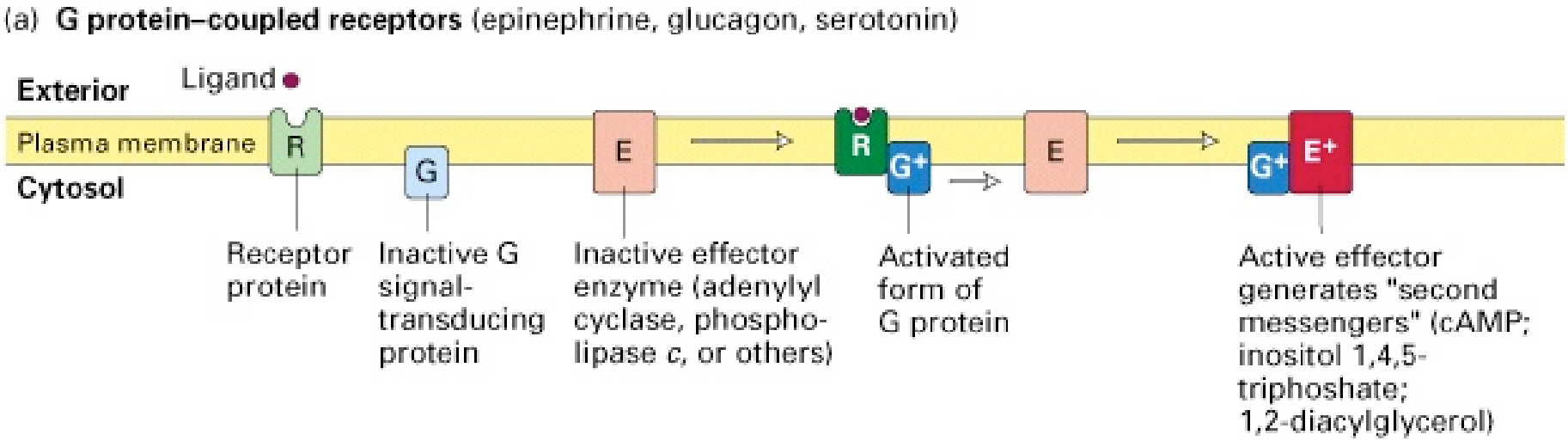




Lodish et al, 2000

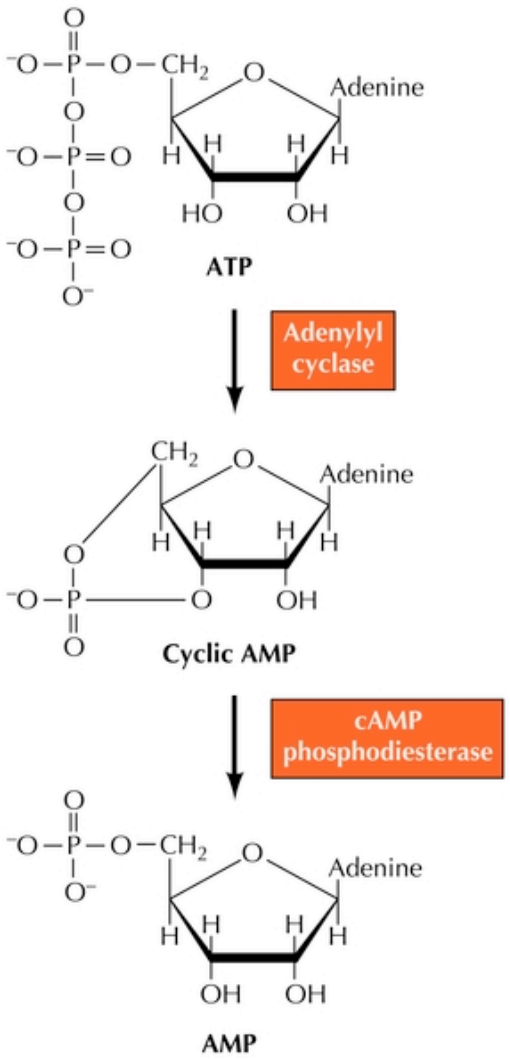
Signal transduction

Seven transmembrane receptors
G proteins



Lodish et al, 2000

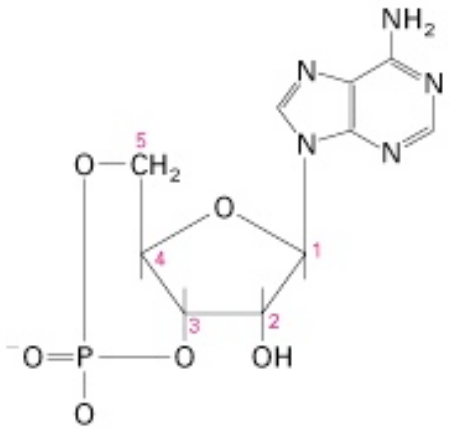
Synthesis of cAMP by adenylate cyclase



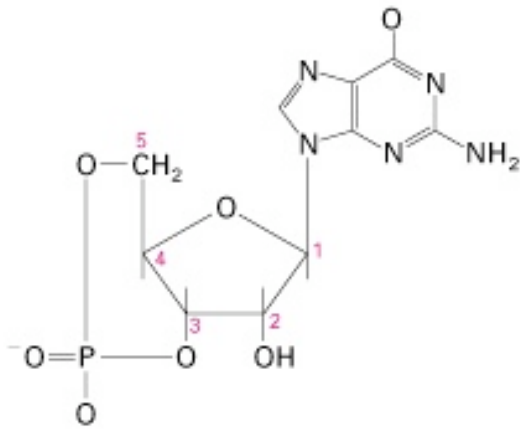
(3'-5'- linkage)

Cooper, 2000

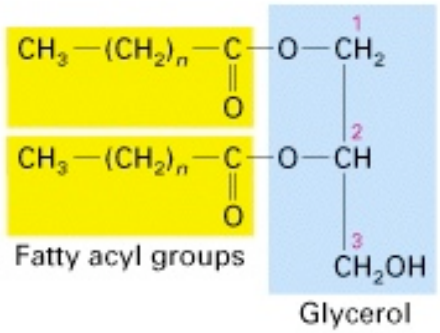
The effects of many hormones are mediated by second messengers



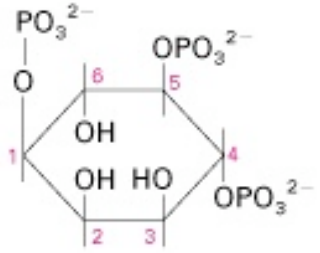
3′,5′-Cyclic AMP
(cAMP)



3′,5′-Cyclic GMP
(cGMP)



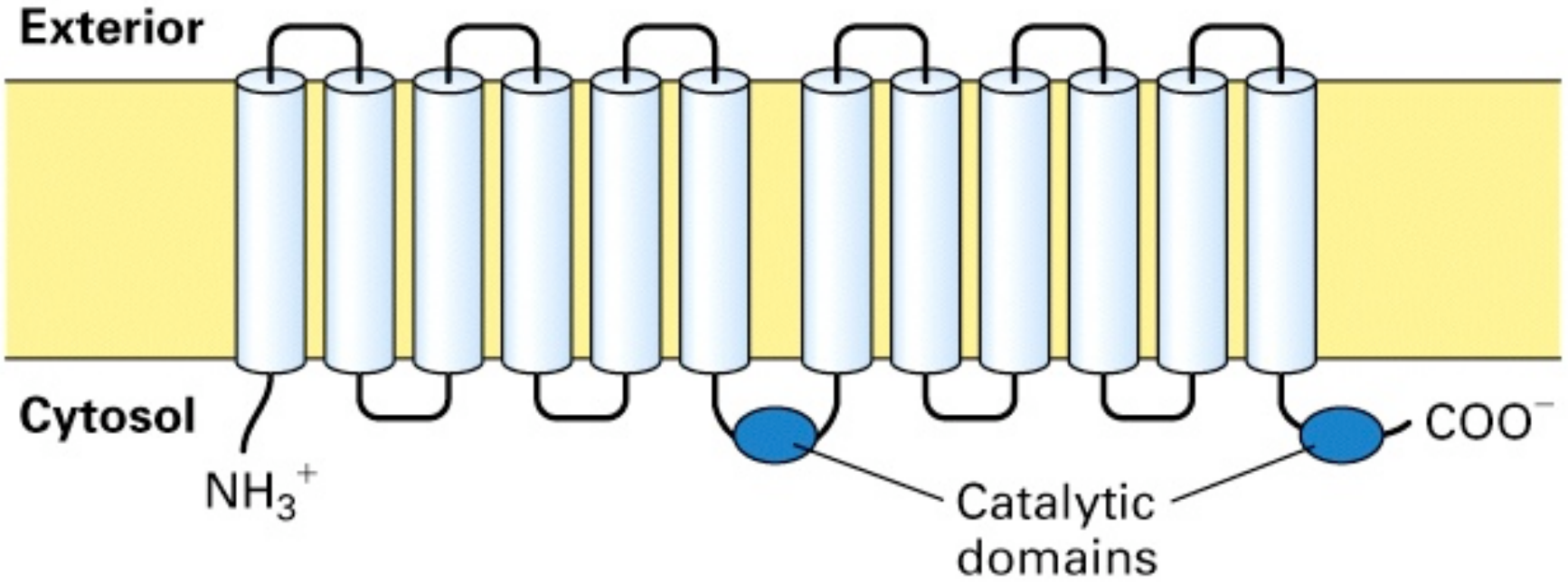
1,2-Diacylglycerol
(DAG)



Inositol
1,4,5-trisphosphate
(IP_3)

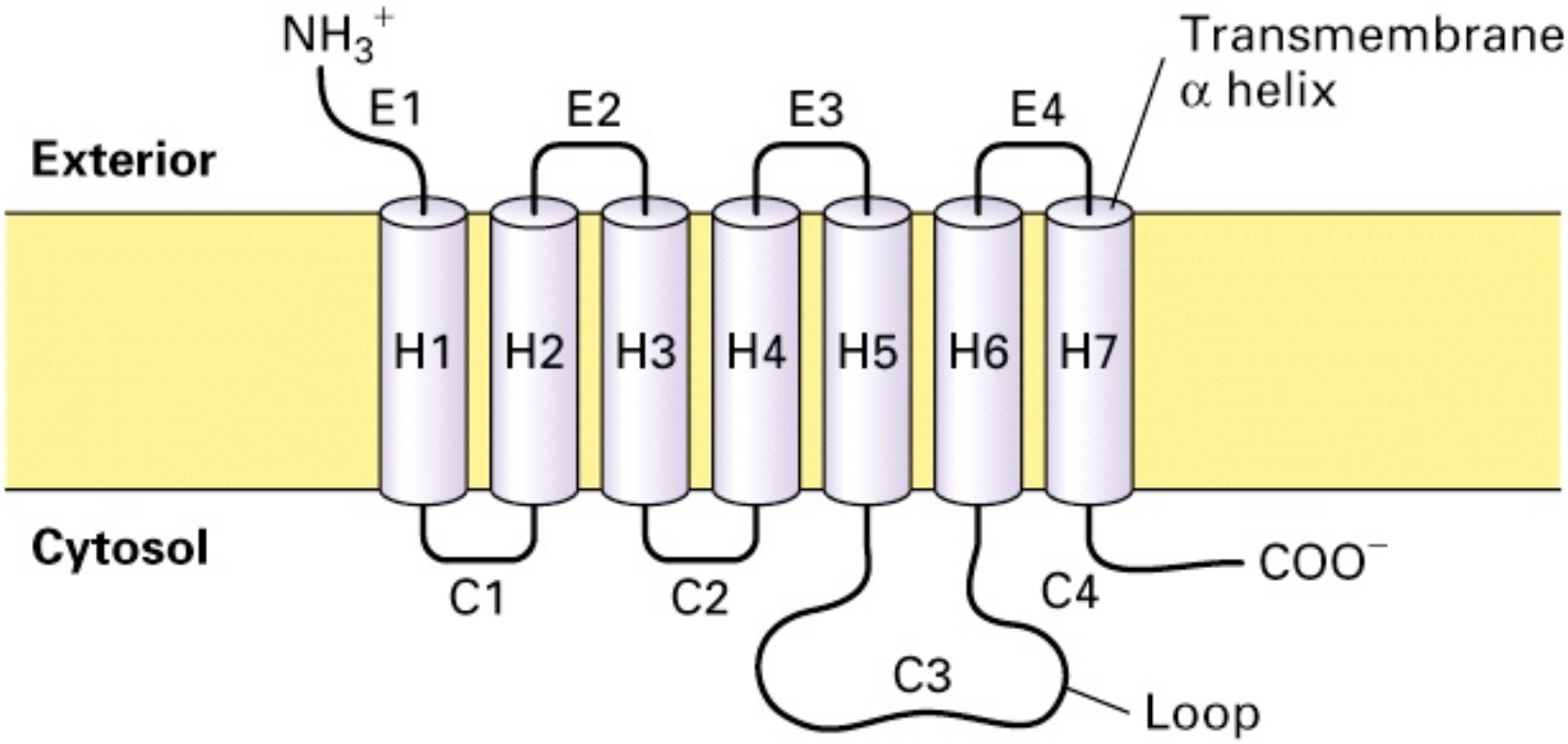
Lodish et al, 2000

Adenylyl cyclase is a membrane-bound enzyme



Lodish et al, 2000

G protein-coupled (7 TM) receptors



Lodish et al, 2000

β-adrenergic effects

-fight or flight response

-increased heart rate and contractility

-vasodilation

-bronchodilation

β_1 and β_2-adrenergic antagonists (β-blockers) are medically important

-hypertension

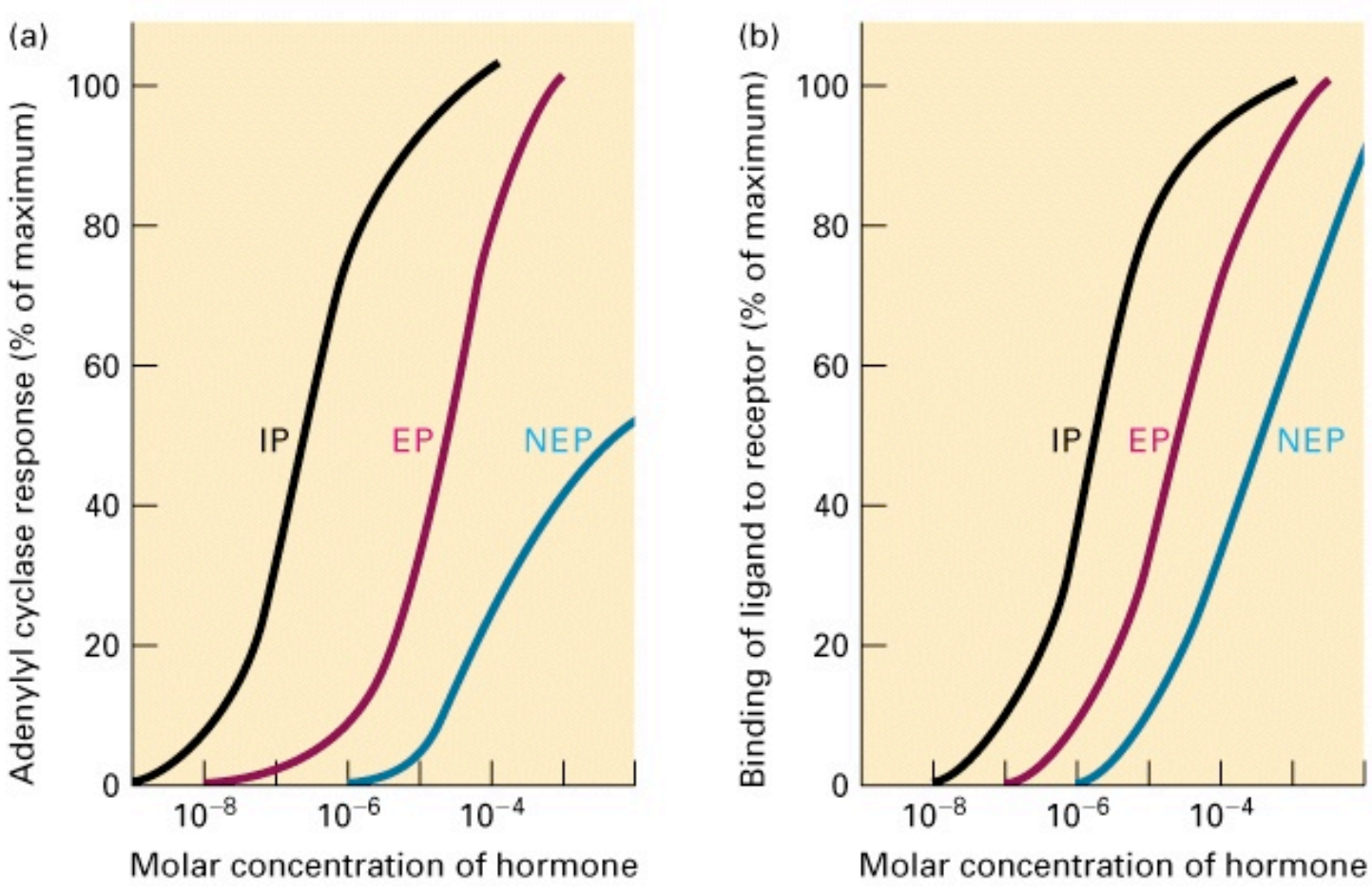
-ischemic heart disease

-arrhythmias

-asthma

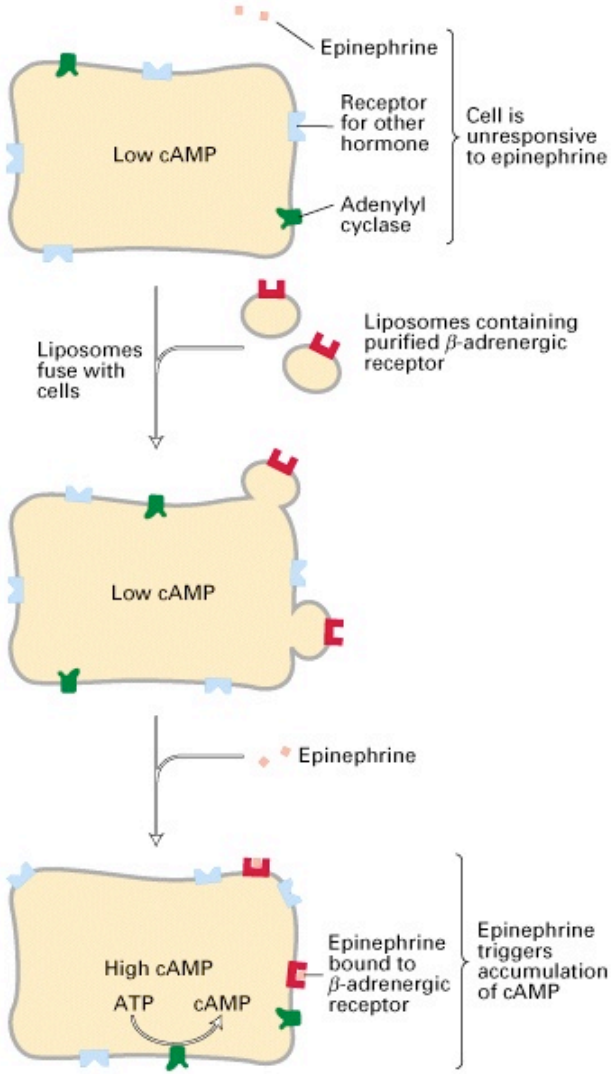
-preterm labor

Stimulation of β-adrenergic receptors leads to a rise in cAMP



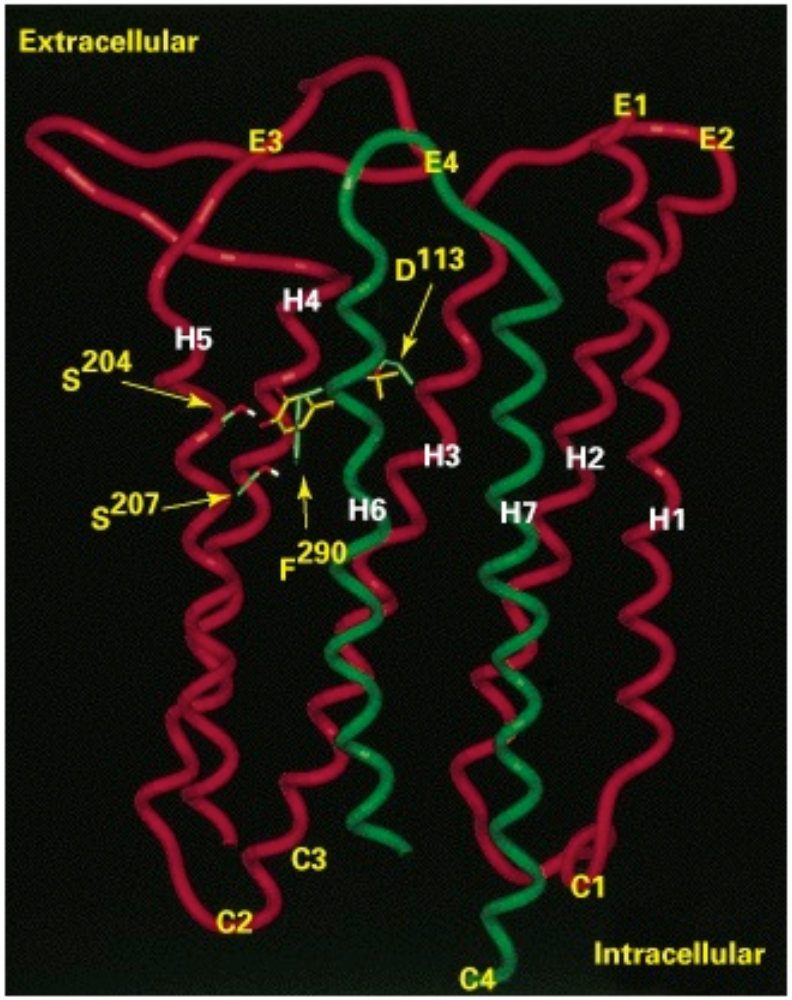
Lodish et al, 2000

-adrenergic receptors mediate the induction of cAMP synthesis



Lodish et al, 2000

Model of complex formed between isoproterenol and the β_2-adrenergic receptor



Lodish et al, 2000

Other important G-protein coupled receptors

Muscarinic receptor (acetylcholine)

important in brain, sympathetic nervous system, heart

Metabotropic glutamate receptor (glutamate)

important in brain

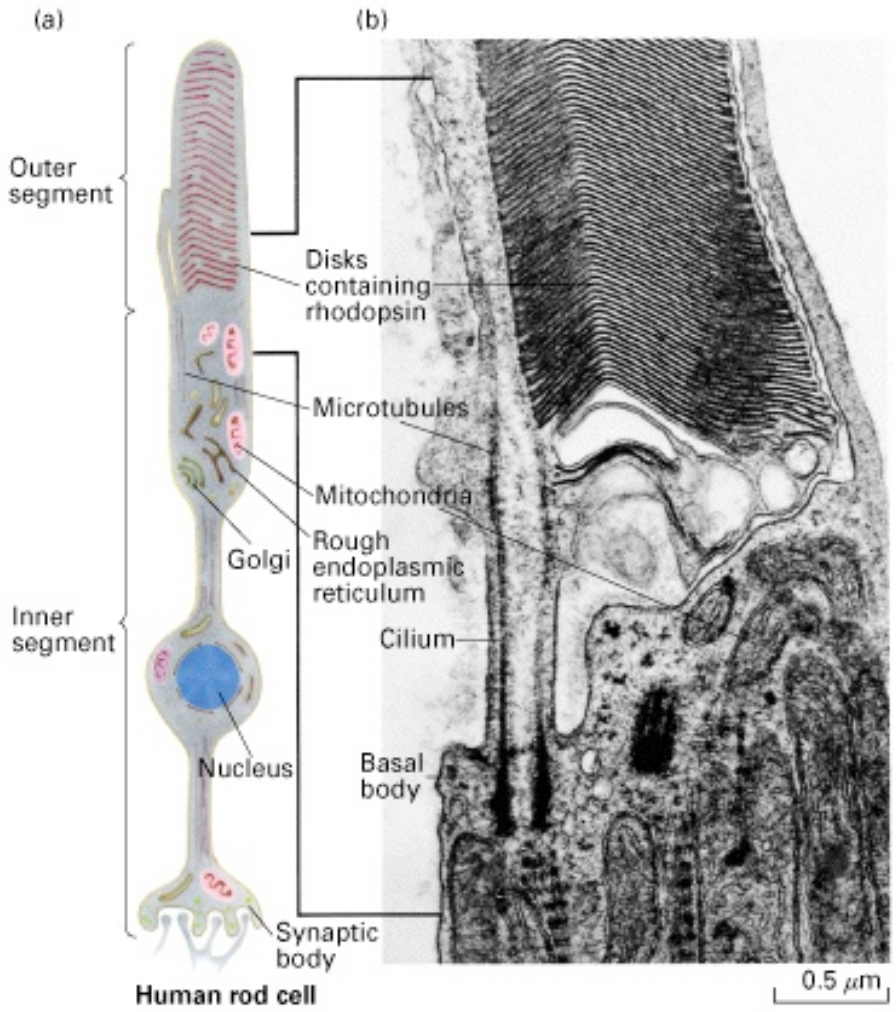
A variety of peptide receptors (ie. Peptide Y, Substance P)

mediators of neural signals in gut, brain, and spinal cord

Odorant receptors

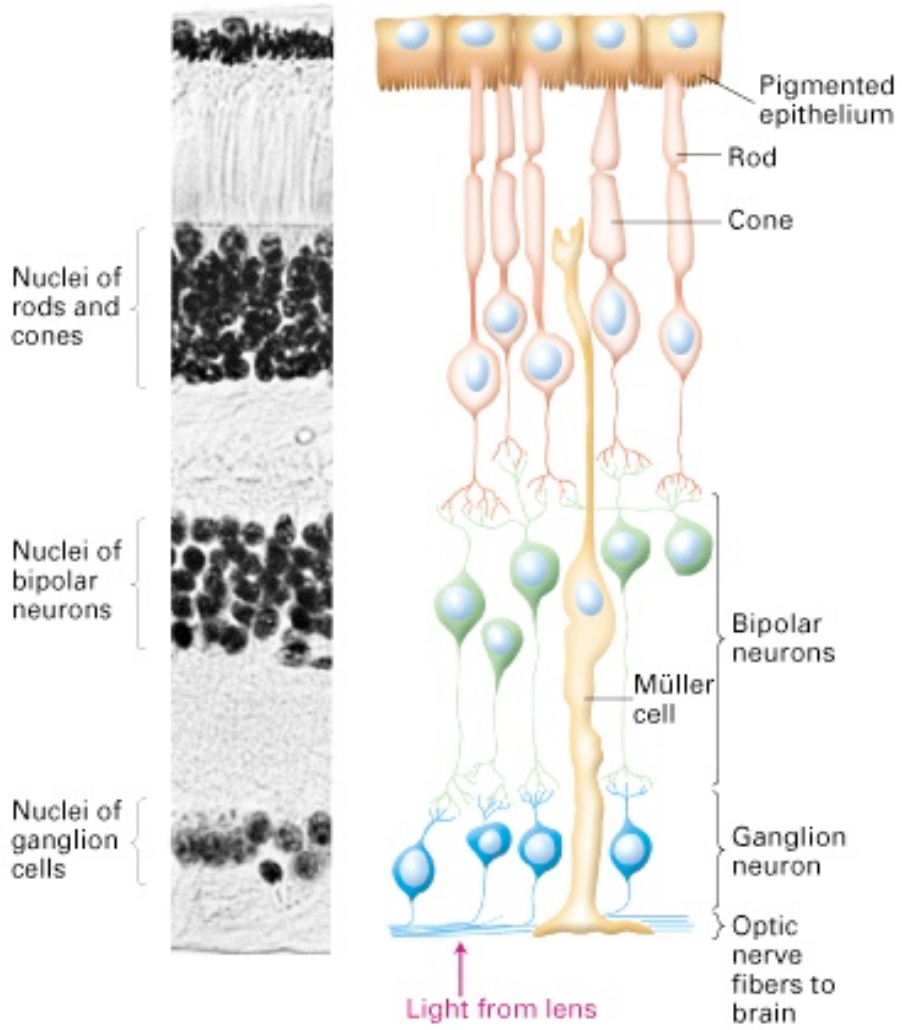
sensory receptors in the nasal epithelium

Membrane disks in the outer segments of rod cells contain rhodopsin, a light-sensitive protein



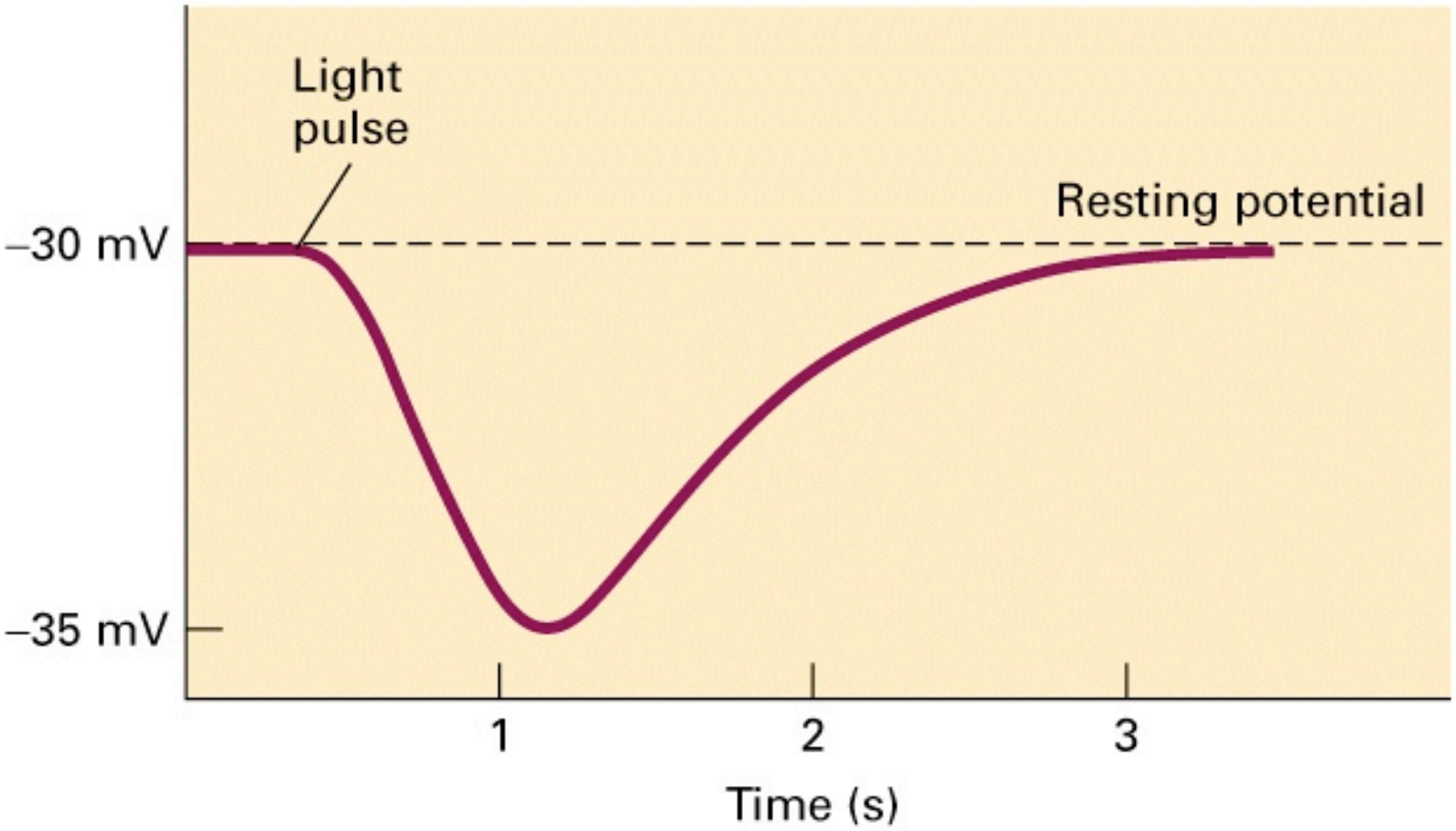
Lodish et al, 2000

Rods and cones contain vision receptors



Lodish et al, 2000

The light-triggered closing of Na^+ channels hyperpolarizes rod cells



Lodish et al, 2000

Absorption of a photon triggers isomerization of retinal and activation of opsin

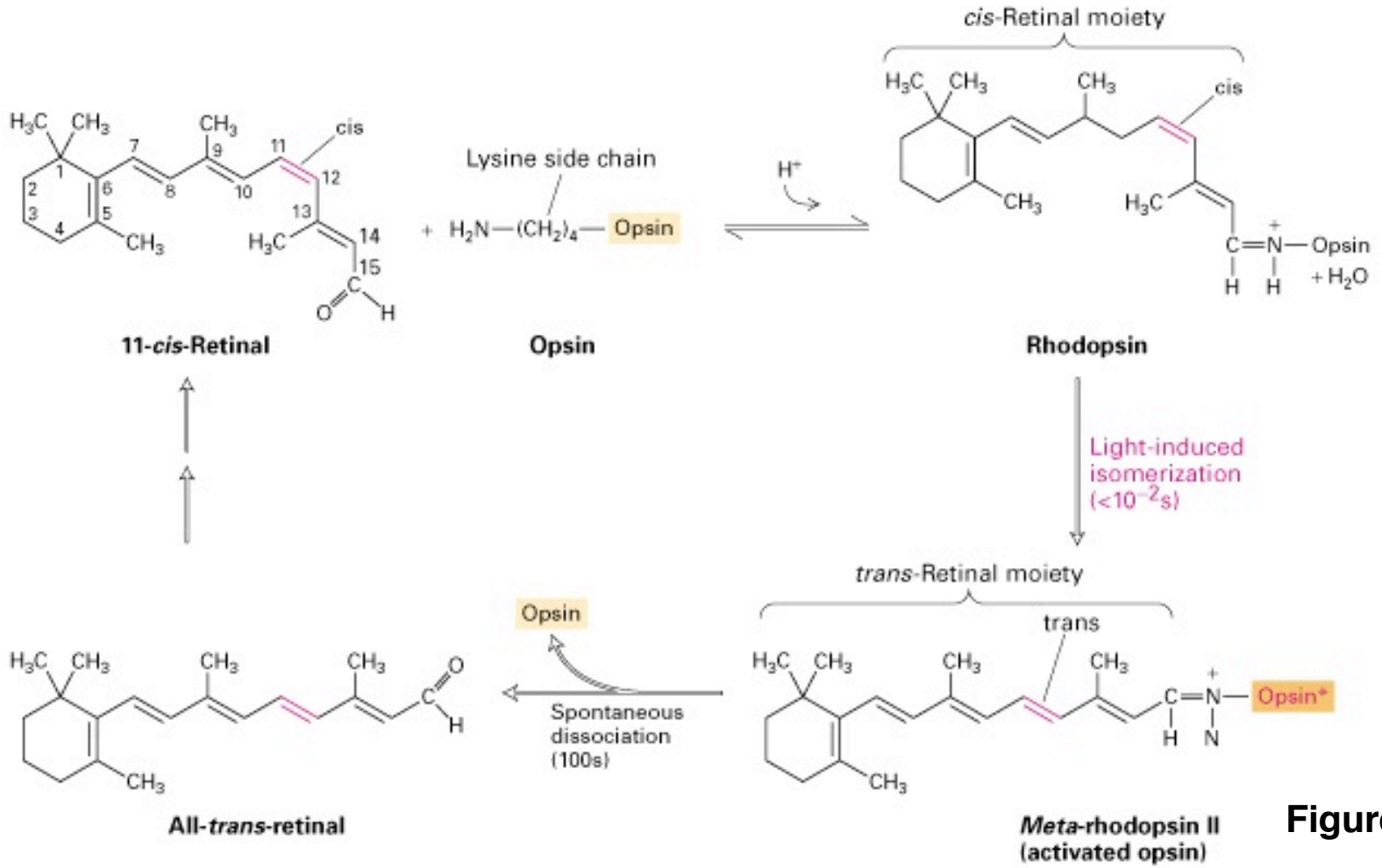
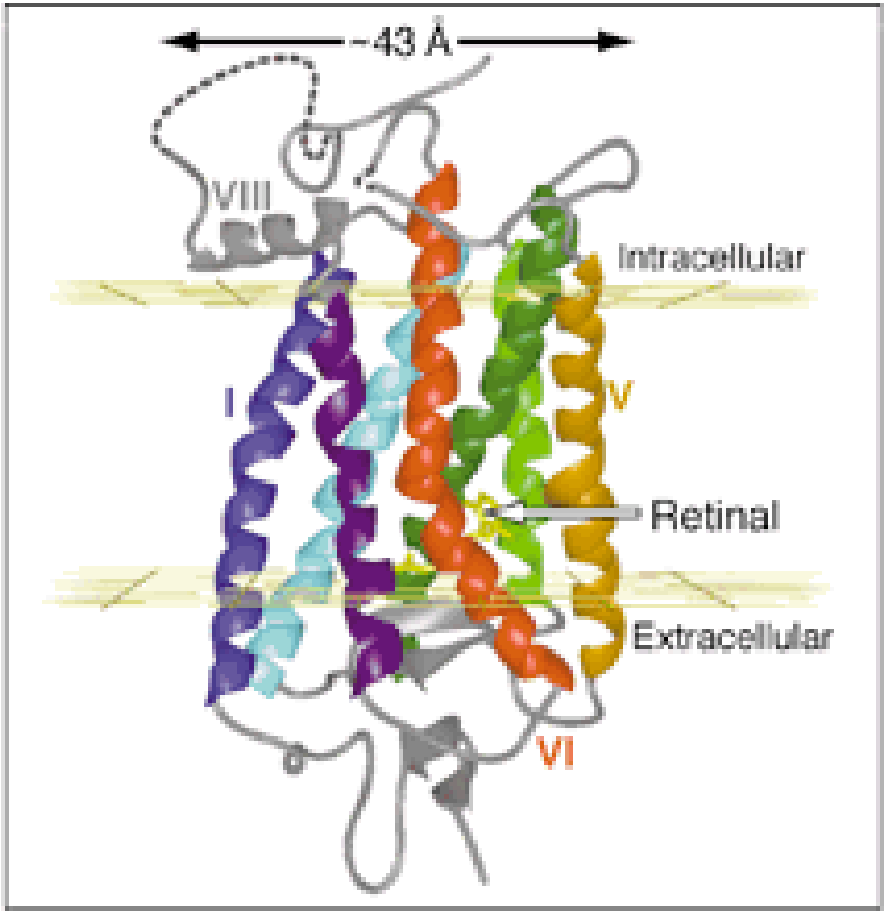
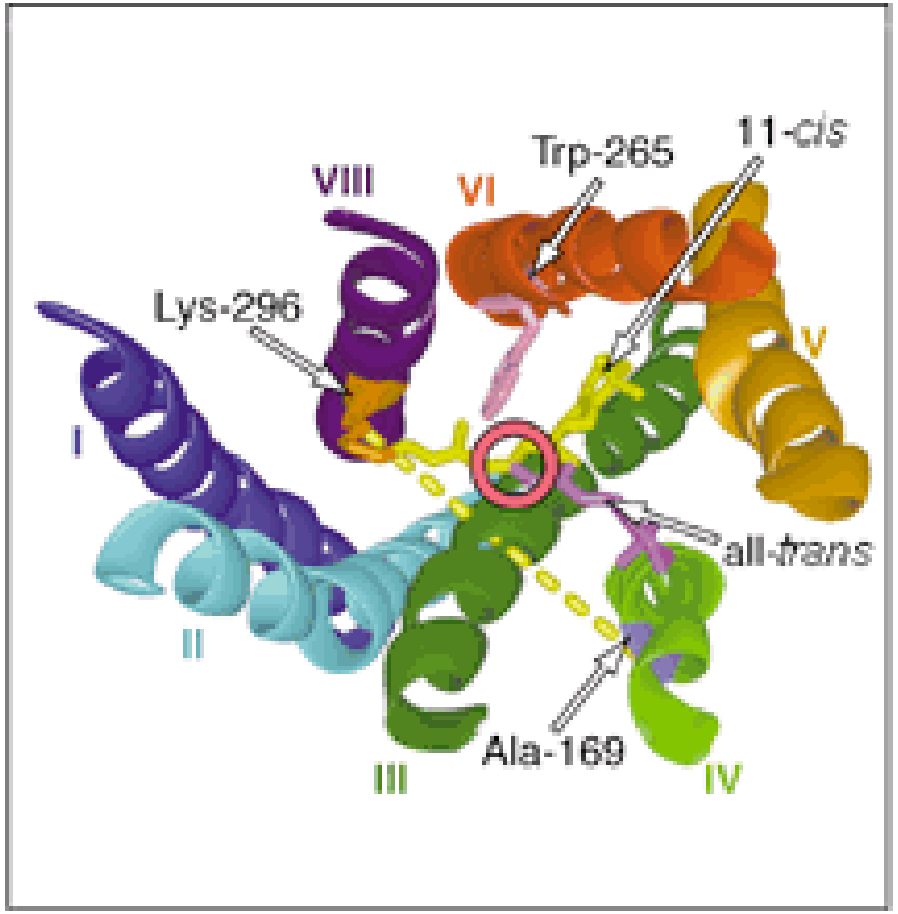


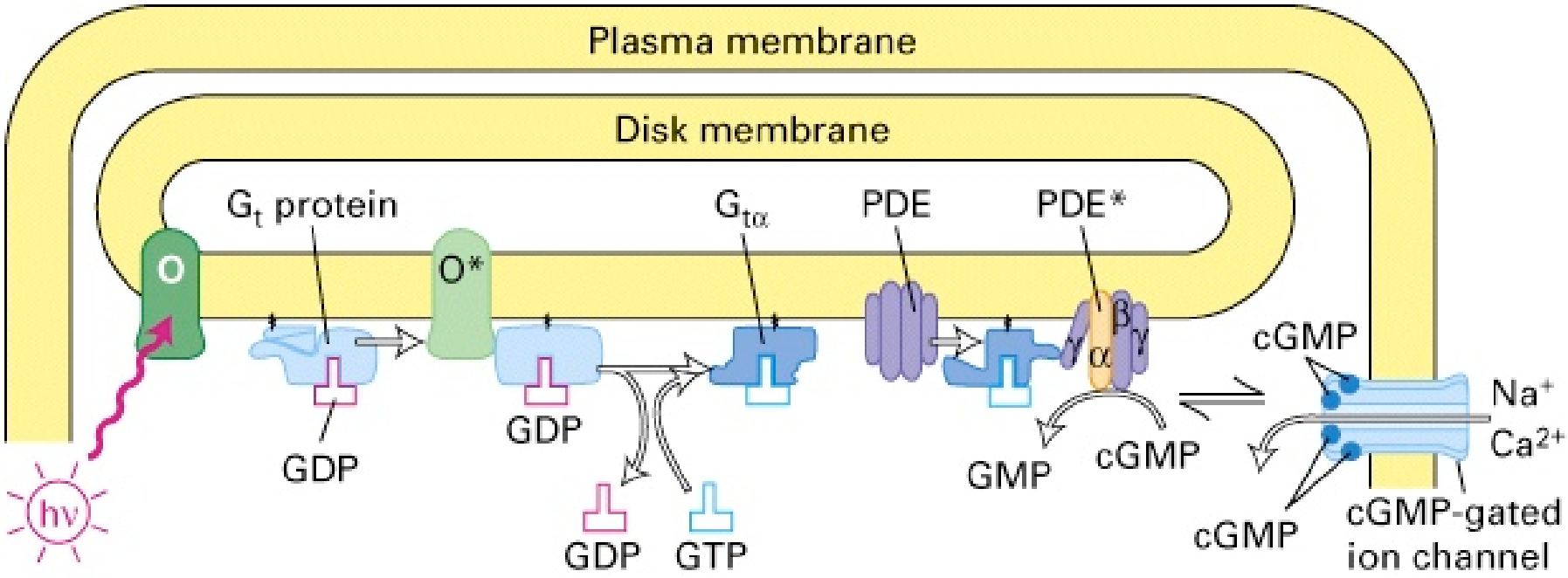
Figure 21-46

Structure of rhodopsin and possible conformational changes





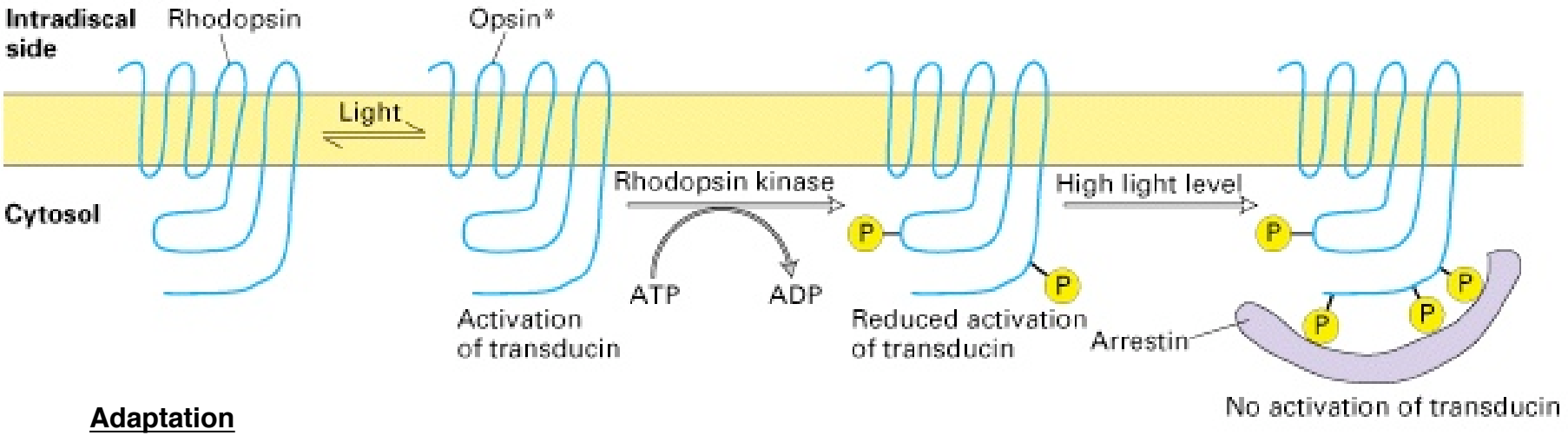
Light activates rhodopsin/Gs/phosphodiesterase and hydrolyzes cGMP



Channel closes upon light activation

Guanylate cyclase regenerates cGMP

Rod cells adapt to varying levels of ambient light



Adaptation

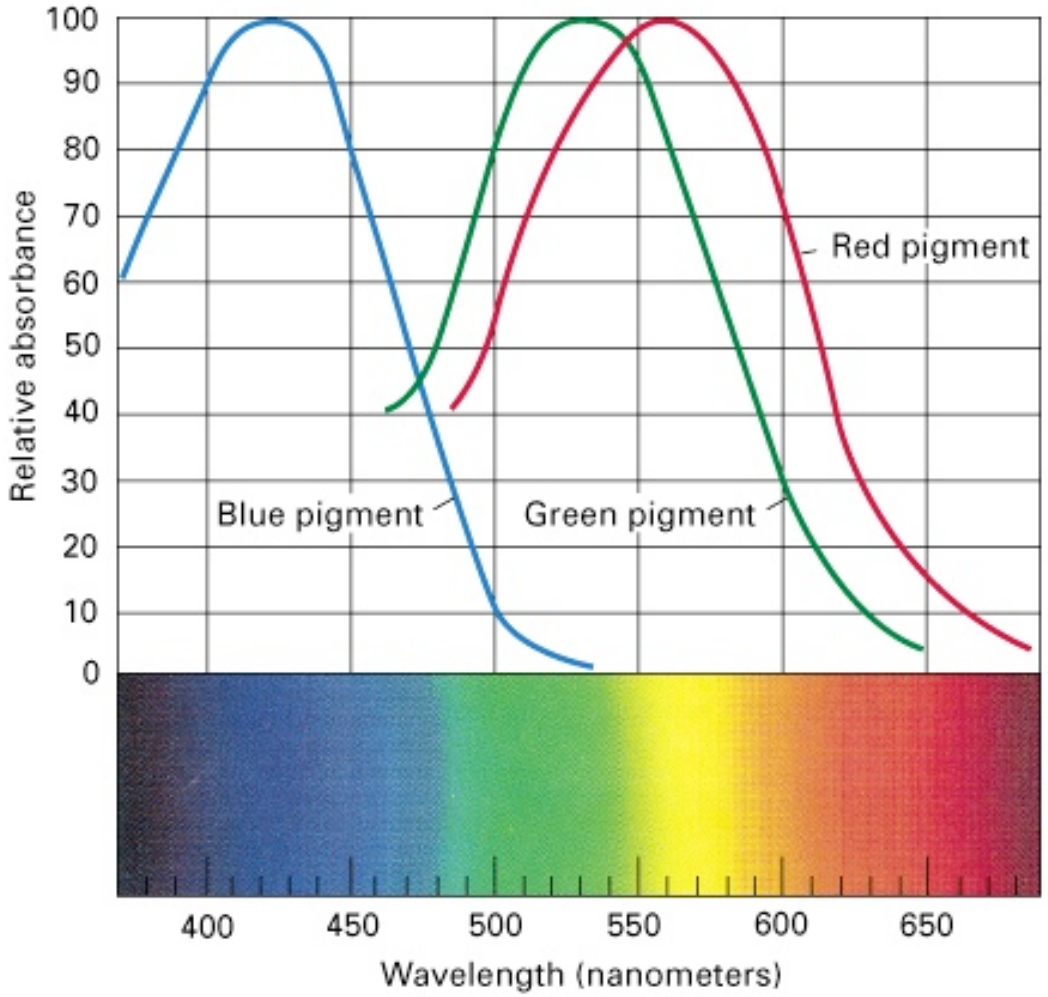
-Rhodopsin kinase phosphorylates activated rhodopsin (up to 7 sites)

-Phosphorylated rhodopsin is less efficient in activating transducin

-At high phosphorylation levels, arrestin binds rhodopsin and prevents binding of transducin

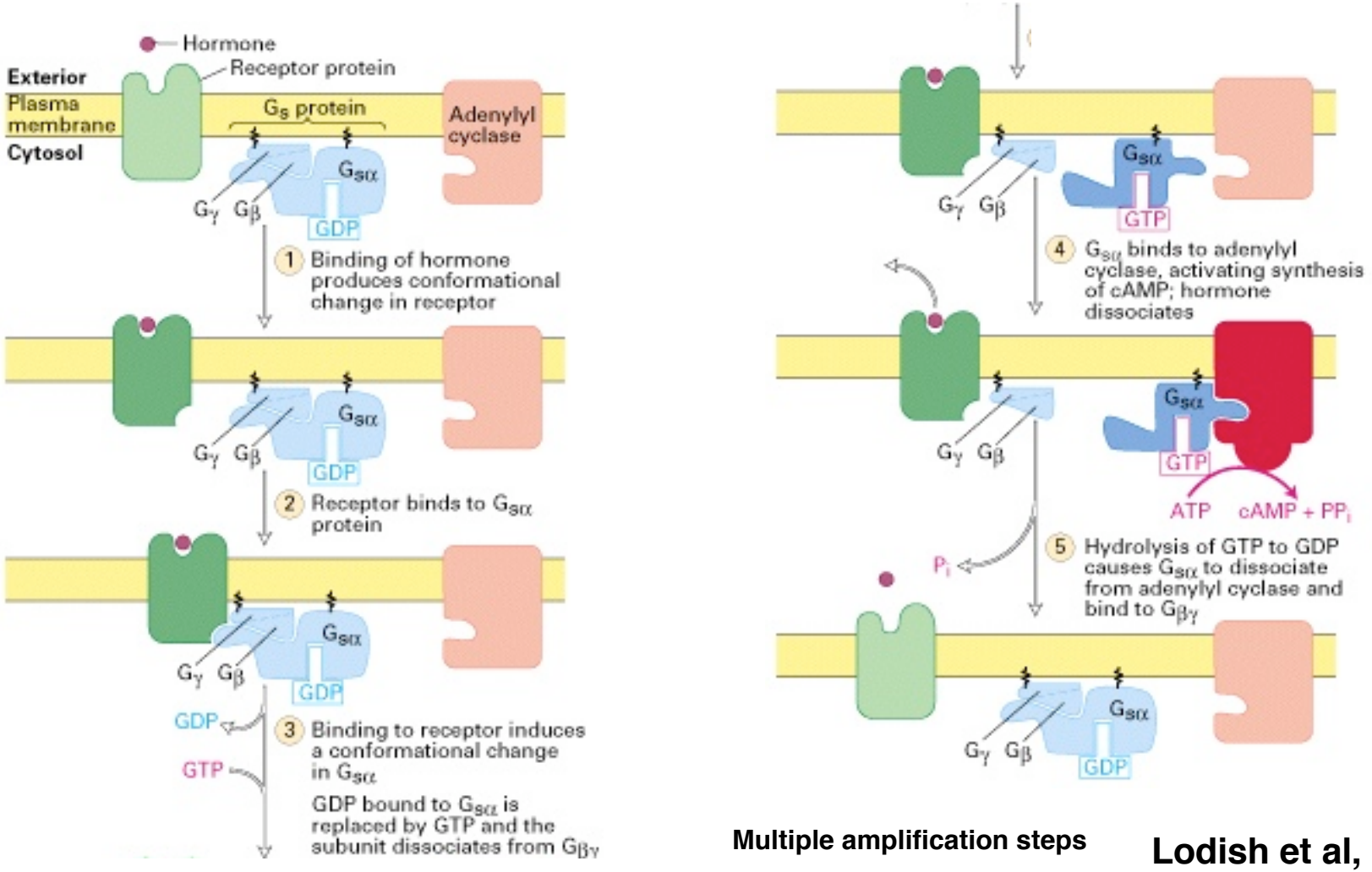
Lodish et al, 2000

Color vision utilizes three opsin pigments



Lodish et al, 2000

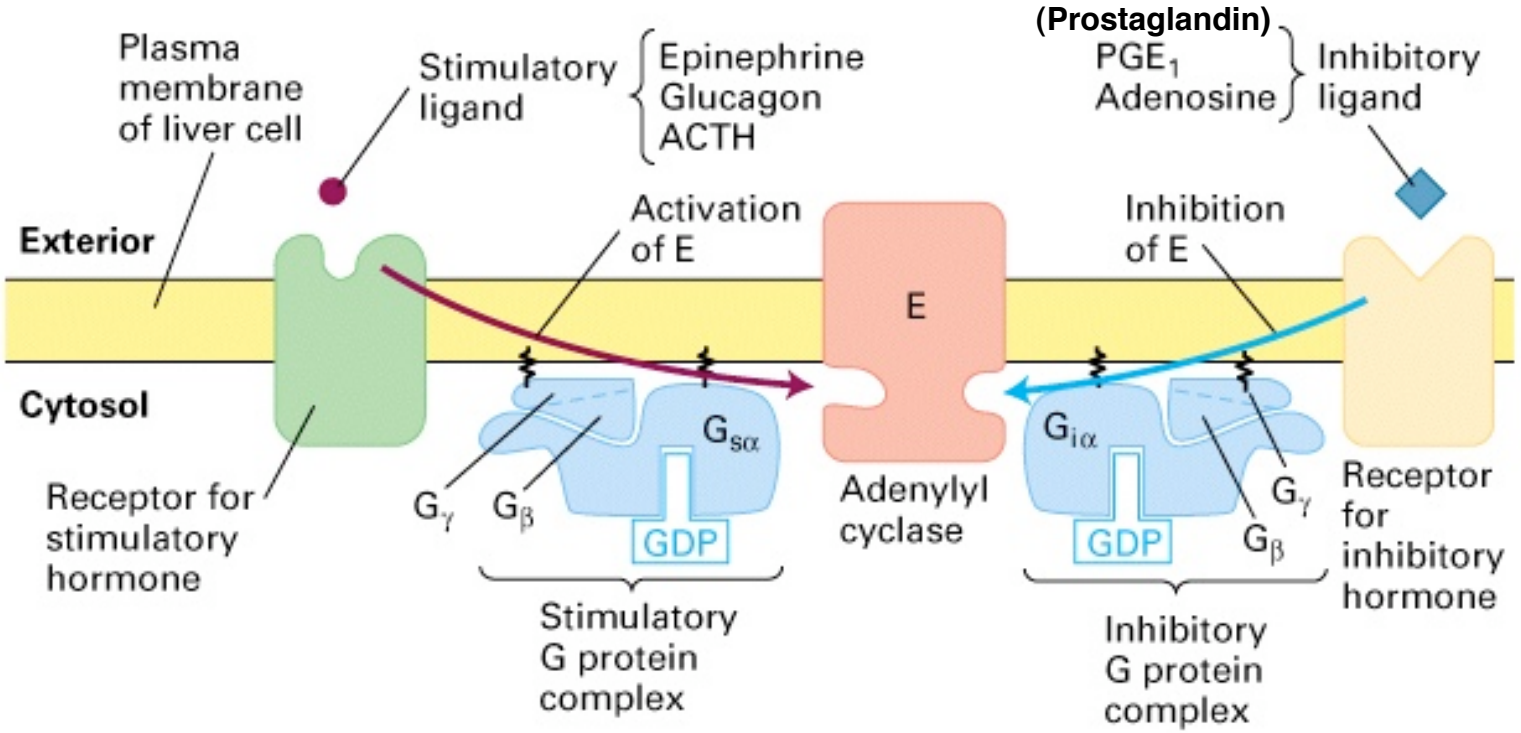
Trimeric G protein links β-adrenergic receptors and adenylyl cyclase



Multiple amplification steps

Lodish et al, 2000

Adenylyl cyclase is stimulated and inhibited by different receptor-ligand complexes



Lodish et al, 2000

Cholera: a diarrheal disease

A acute diarrheal disease

- massive watery diarrhea
- vomiting
- adults can lose up to 1 L/hr

V. cholera infections cause unregulated adenylate cyclase in intestinal cells

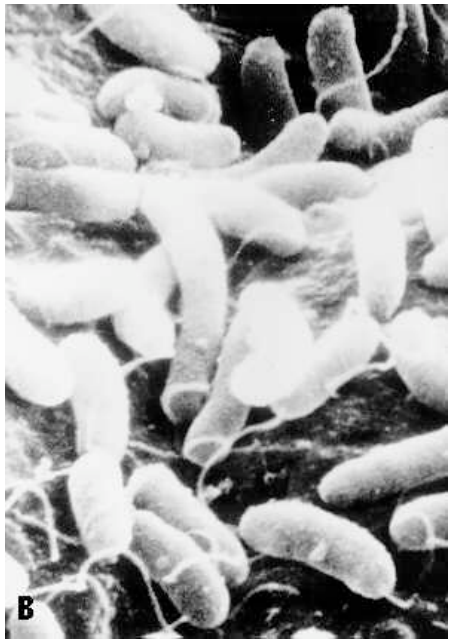
Vibrio cholera- gram negative rod (bacterium)

Native to Ganges river in India; 7 pandemics in since 1911

Transmission- fecal contamination of water: Vibrio ingested, colonizes small bowel, produces cholera toxin

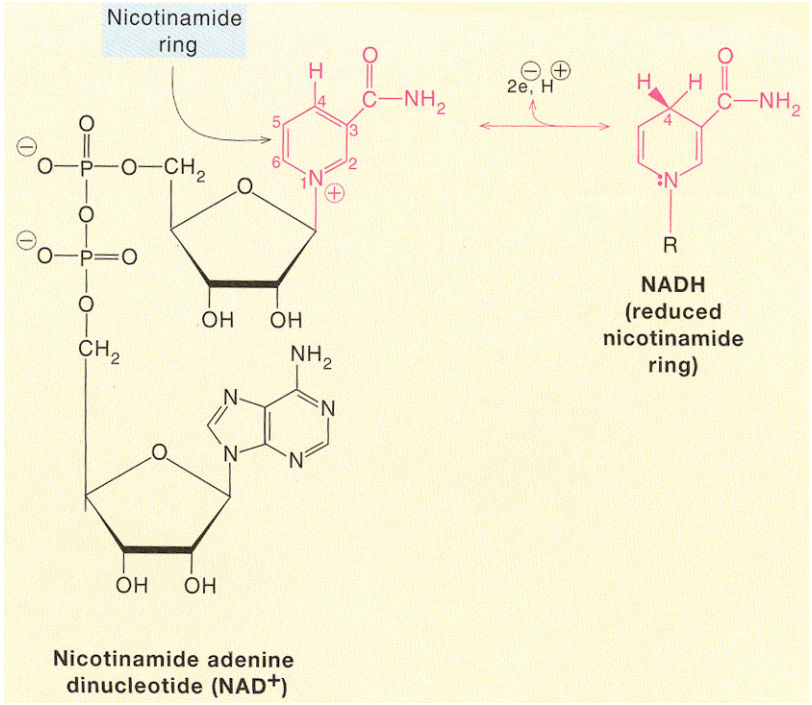
Cholera toxin catalytically transfers ADP-ribose from NAD (nicotine adenine dinucleotide) to G_s protein

G_s is permanently upregulated, leading to excess adenylate cyclase activity

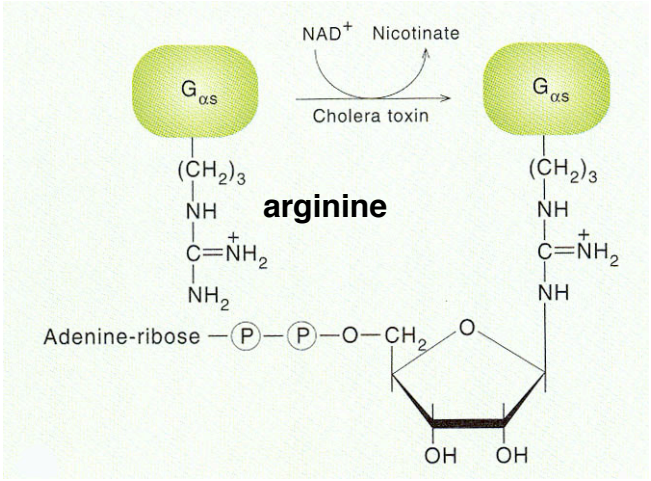


ADP-ribosylation of G_s protein by cholera toxin

Nicotine adenine dinucleotide (NAD)



ADP-ribosylation



ADP-ribose is added to an arginine residue in Gs

Blocks GTPase activity

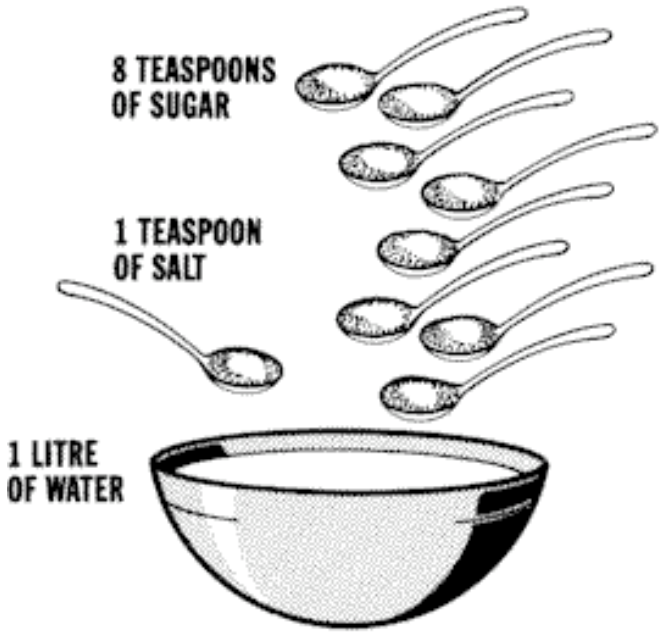
Most cholera patients recover with oral rehydration therapy

-NaCl accumulates in intestinal lumen; massive water loss/diarrhea

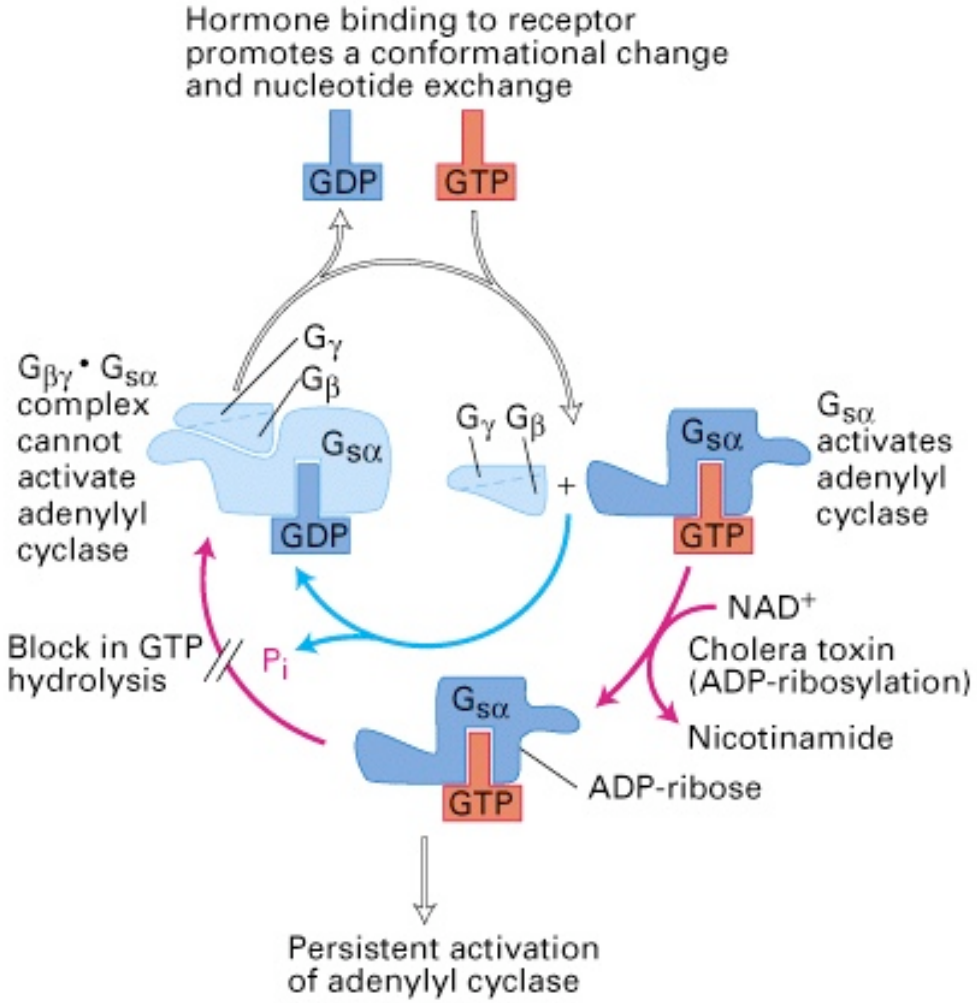
-Intestinal muscosa intact

-untreated, up to 50% death (dehydration/hypovolemic shock)

-with glucose/electrolyte replacement therapy, less than 1% death



Some bacterial toxins irreversibly modify G proteins



Also, pertussis toxin ADP-ribosylates Gi and locks Gi in GDP (inactive) state

Lodish et al, 2000