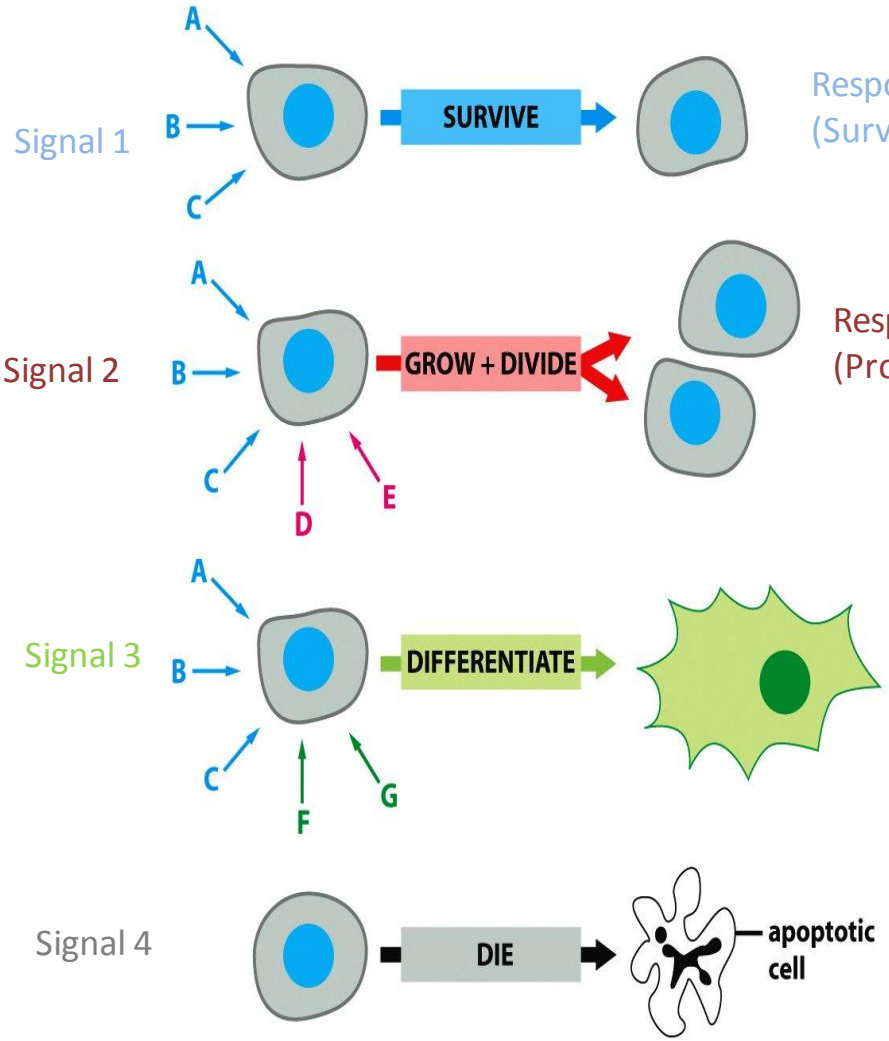
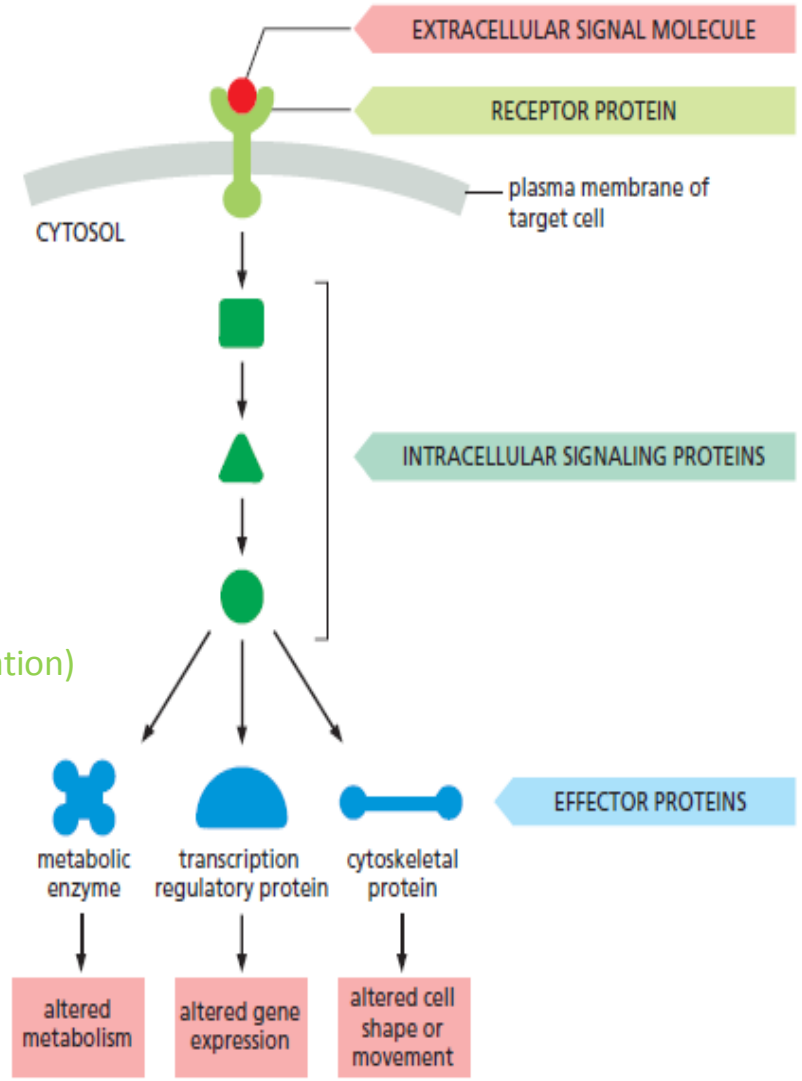
Cell Signaling

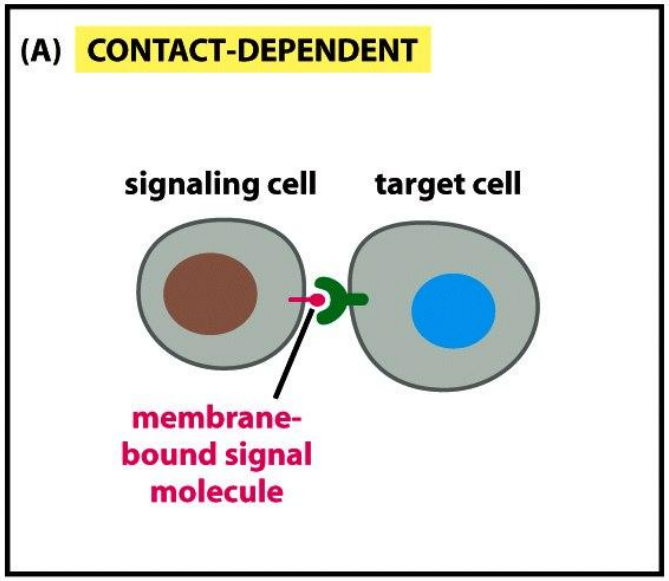
Principles of Signaling

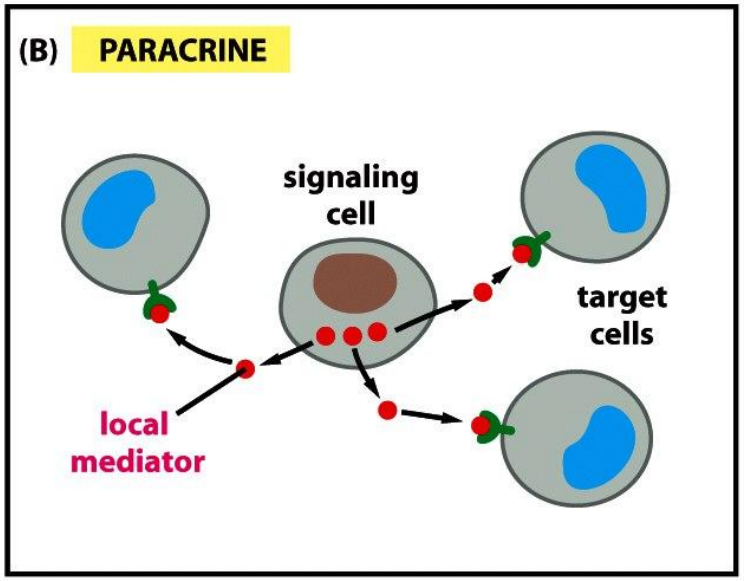


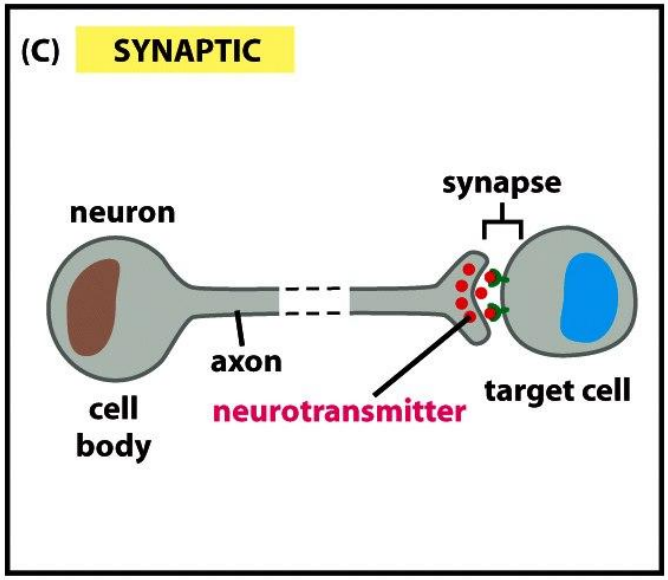


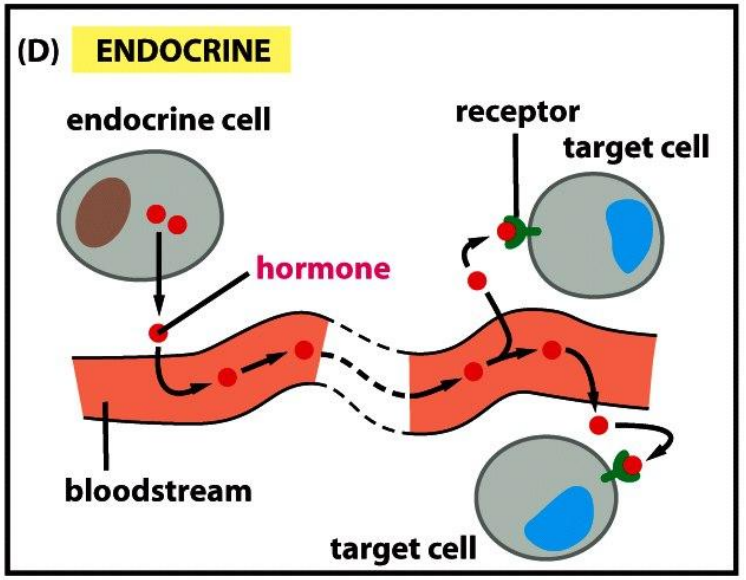
Types

- ✓ Endocrine
- ✓ Paracrine
- ✓ Autocrine
- ✓ Juxtacrine

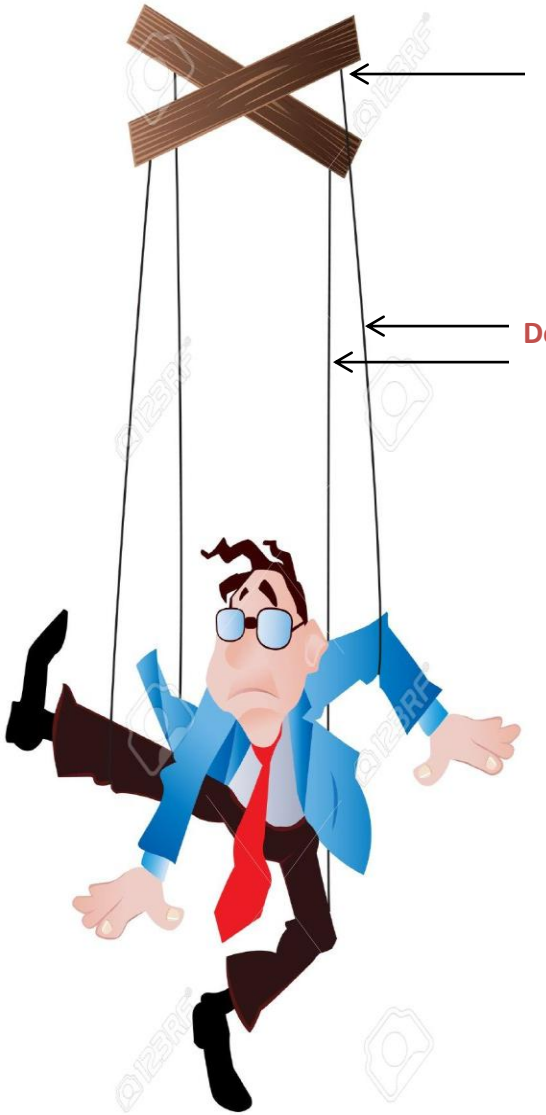






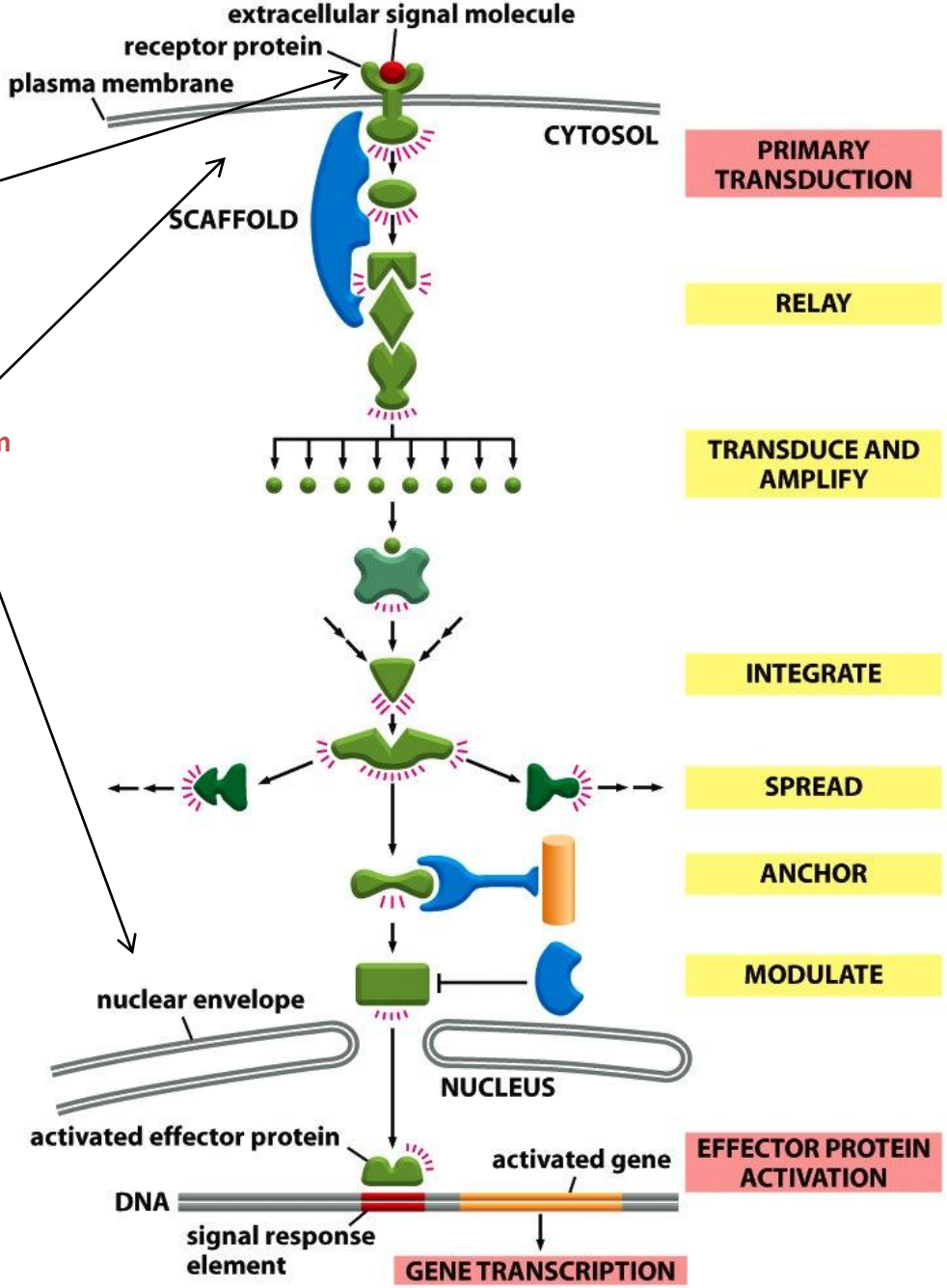


Mechanism of Signal Transduction



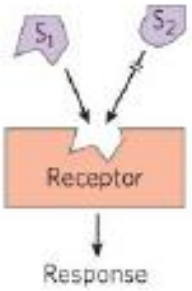
Receptor

Down stream molecular cascade

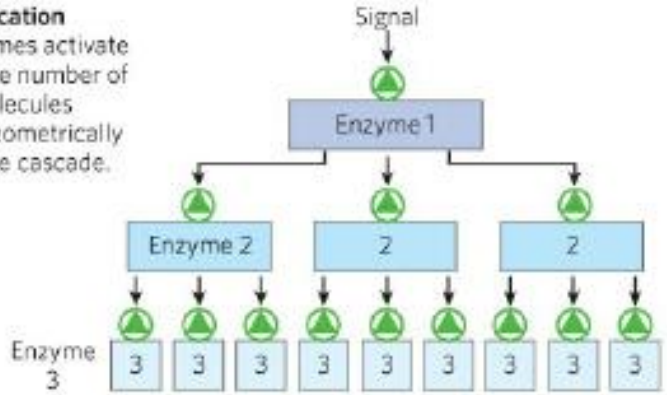


Properties of Signal Transduction

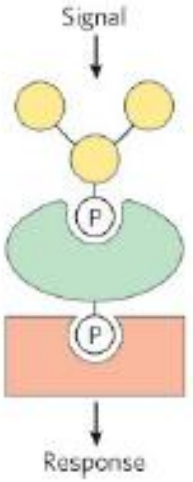
(a) Specificity
Signal molecule fits binding site on its complementary receptor; other signals do not fit.



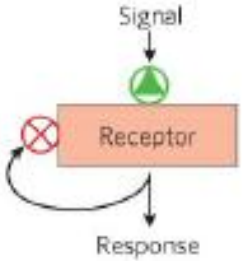
(b) Amplification
When enzymes activate enzymes, the number of affected molecules increases geometrically in an enzyme cascade.



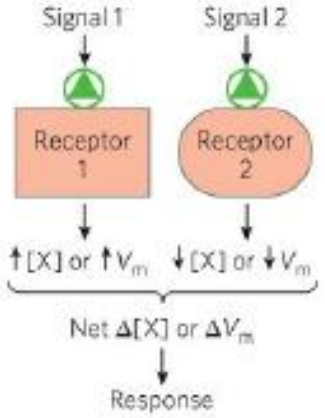
(c) Modularity
Proteins with multivalent affinities form diverse signaling complexes from interchangeable parts. Phosphorylation provides reversible points of interaction.



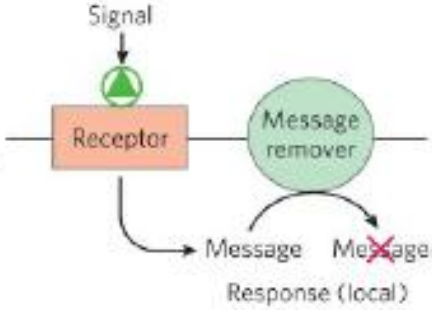
(d) Desensitization/Adaptation
Receptor activation triggers a feedback circuit that shuts off the receptor or removes it from the cell surface.



(e) Integration
When two signals have opposite effects on a metabolic characteristic such as the concentration of a second messenger X, or the membrane potential V_m, the regulatory outcome results from the integrated input from both receptors.



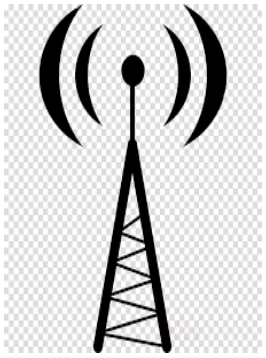
(f) Localized response
When the enzyme that destroys an intracellular message is clustered with the message producer, the message is degraded before it can diffuse to distant points, so the response is only local and brief.

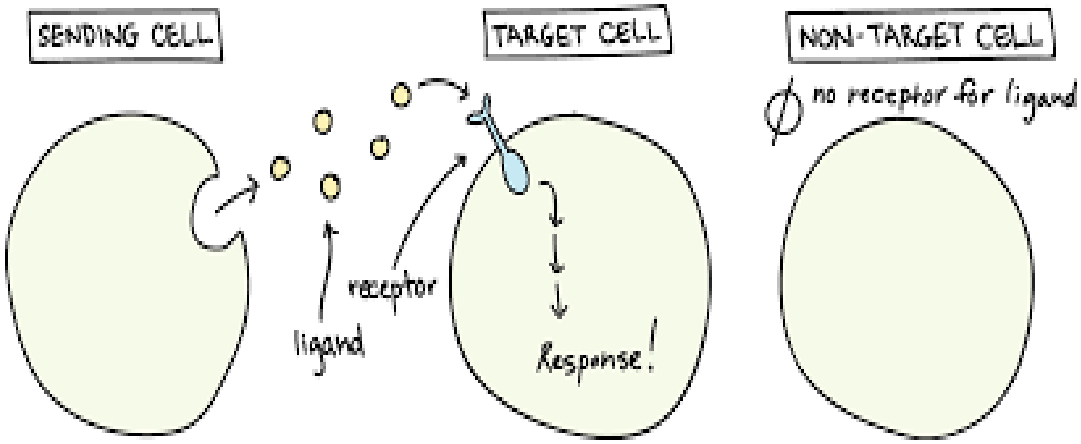


Receptor

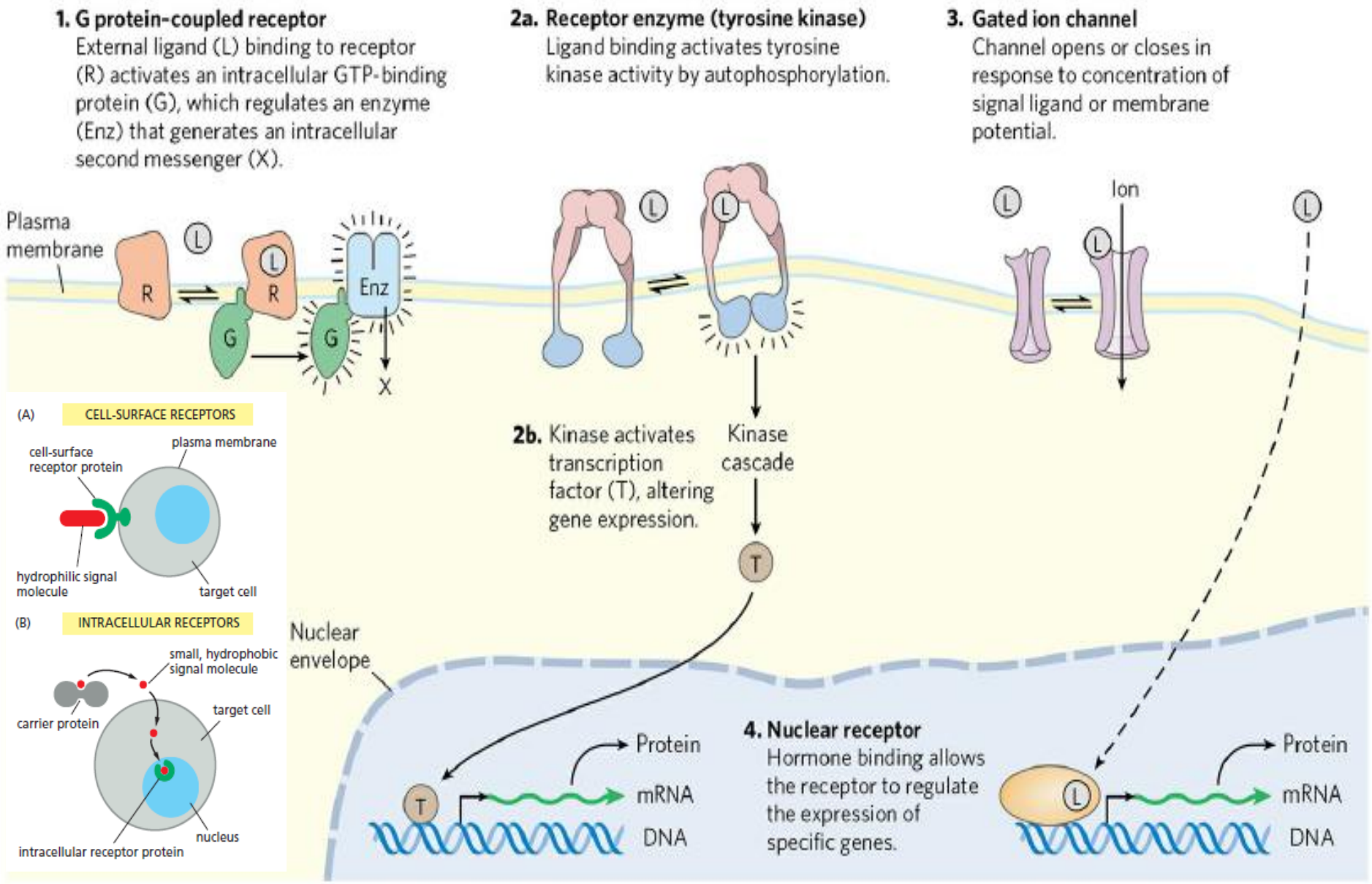
- A Receptor is a protein, which acts as a receiver of different sorts of ligands (signals).
- Ligands are also bio-molecules
- Ligands binds reversibly (non-covalently) with receptors (R-L Complex)
- When the R-L complex forms the receptor proteins becomes activated and evokes a response
- Since receptor converts the binding energy into other forms as response, the phenomena is also known as **signal transduction**
- Activated receptors, activates specific intracellular down stream molecules (signaling pathway/cascade)
- Specific pathway ultimately evokes different response depending upon, which Receptor it activates and which signaling pathway is involved.

Signal sender





Classification of Receptor



Different Ligands and Receptors

Nature	Receptor
Protein/peptide	Extracellular
Steroids	Cytosol/Nucleus
Catecholamines	Extracellular
T3/T4	Nuclear
Melatonin	Exracellular
Eicosanoids	Extracellular

TABLE 3-1
Hormones That Work on the Cell Surface

Peptides and Proteins

Adrenocorticotropic hormone (ACTH)
Anterior pituitary thyrotropin or thyroid-stimulating hormone (TSH)
Antidiuretic hormone (ADH)
Atrial natriuretic peptide (ANP)
Calcitonin
Cholecystokinin
Corticotropin-releasing hormone (CRH)
Follicle-stimulating hormone (FSH)
Gastrin
Glucagon
Gonadotropin-releasing hormone (GnRH)
Growth hormone (GH)
Growth hormone–releasing hormone (GHRH)
Insulin
Insulin-like growth factor 1 (IGF-1)
Luteinizing hormone (LH)
Oxytocin
Parathyroid hormone (PTH)
Prolactin (PRL)
Secretin
Somatostatin (SS)
Thyrotropin-releasing hormone (TRH)

Molecules Derived From Amino Acids

Dopamine (inhibits prolactin)
Epinephrine (also called adrenaline)
Norepinephrine (also called noradrenaline)
Serotonin

Eicosanoids

Prostaglandins: PGA_1, PGA_2, PGE_2

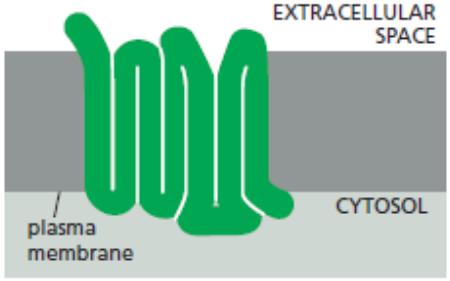
TABLE 3-4
Nuclear Receptor Ligands and Their Receptors

Ligand	Receptor
Classic Hormones	
Thyroid hormone	Thyroid hormone receptor (TR), subtypes α, β
Estrogen	Estrogen receptor (ER), subtypes α, β
Testosterone	Androgen receptor (AR)
Progesterone	Progesterone receptor (PR)
Aldosterone	Mineralocorticoid receptor (MR)
Cortisol	Glucocorticoid receptor (GR)
Vitamins	
1,25-$(OH)_2$-Vitamin D_3	Vitamin D receptor (VDR)
All-*trans*-retinoic acid	Retinoic acid receptor, subtypes α, β, γ
9-*cis*-Retinoic acid	Retinoid X receptor (RXR), subtypes α, β, γ
Metabolic Intermediates and Products	
Fatty acids	Peroxisome proliferator-activated receptor (PPAR), subtypes α, δ, γ
Oxysterols	Liver X receptor (LXR), subtypes α, β
Bile acids	Bile acid receptor (BAR, also called FXR)
Heme	Rev-Erb subtypes α, β
Phospholipids	Liver receptor homologue-1 (LRH-1) Steroidogenic factor-1 (SF-1)
Xenobiotics	Pregnane X receptor (PXR) Constitutive androstane receptor (CAR)

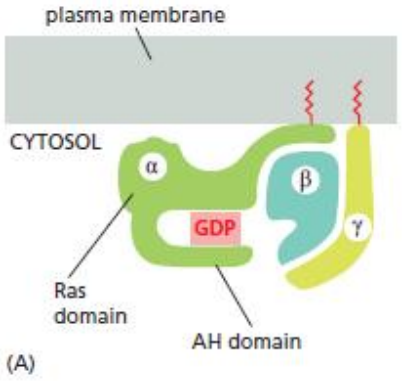
TABLE 3-9
Factors Modulating Receptor Activity in Different Tissues

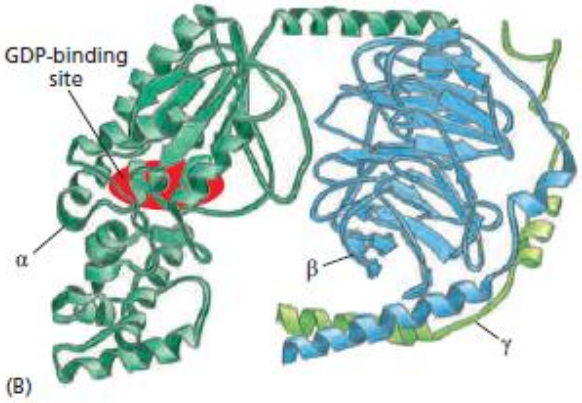
Concentration of receptor
Cell specificity
Variation within a given cell type
Post-translational modification of receptor (e.g., phosphorylation)
Regulation of intracellular ligand levels (see Table 3-5)
Tissue-specific factors that open chromatin
Function of ligand
    Agonist
    Partial agonist
    Antagonist
Concentration and types of coregulators
    Coactivators
    Corepressors

G-Protein coupled receptor



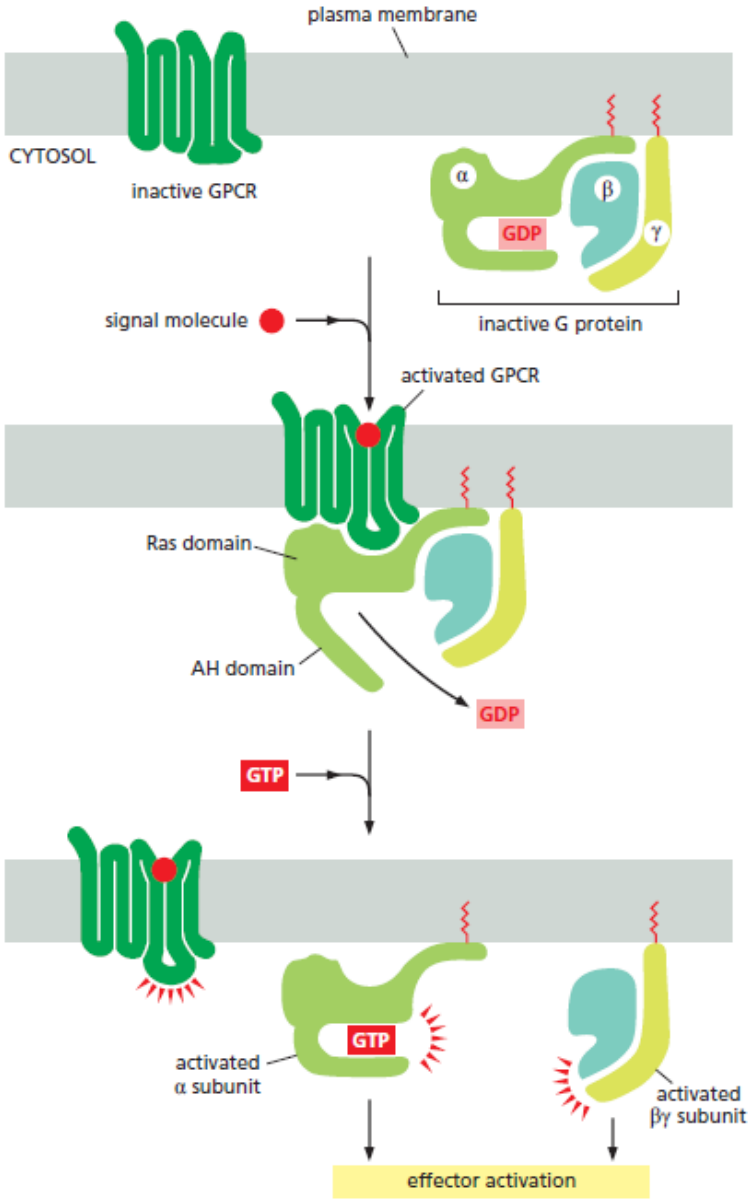
Seven pass G protein coupled Receptor

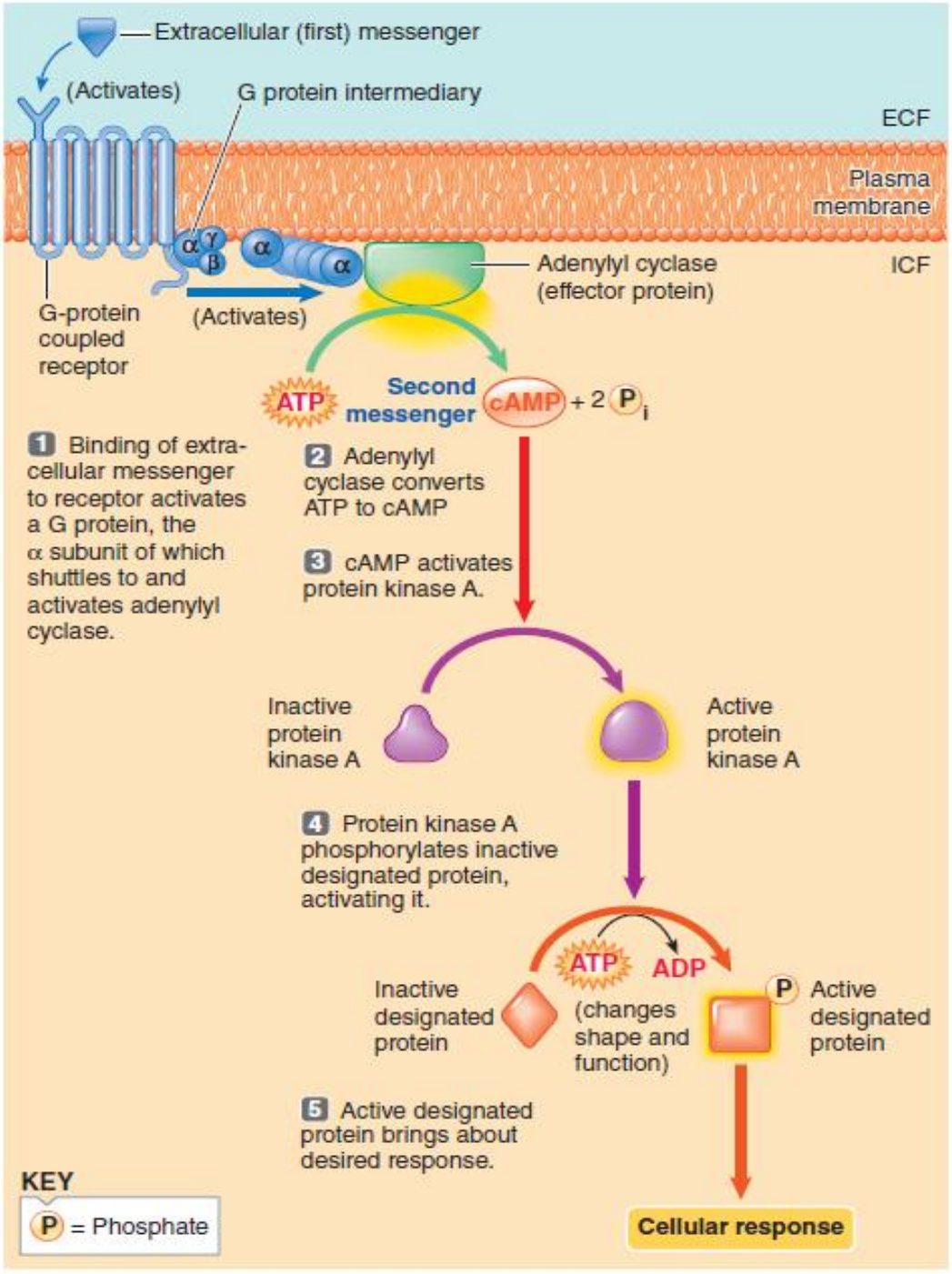


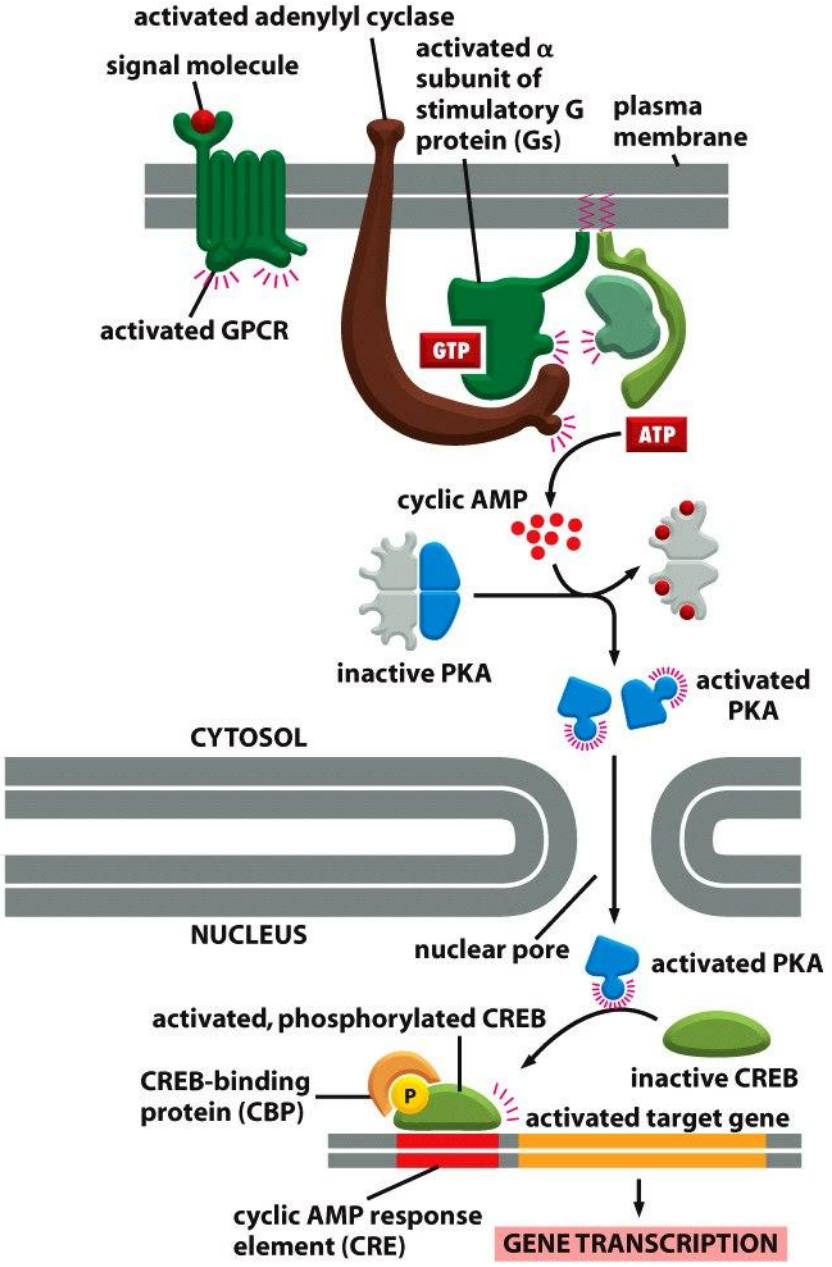


Trimeric G protein

Activation of G protein via GPCR




Extracellular (first) messenger
(Activates)
G protein intermediary
ECF
Plasma membrane
ICF
Adenylyl cyclase (effector protein)
G-protein coupled receptor
(Activates)
ATP
Second messenger
cAMP
+ 2 Pi
1 Binding of extracellular messenger to receptor activates a G protein, the α subunit of which shuttles to and activates adenylyl cyclase.
2 Adenylyl cyclase converts ATP to cAMP
3 cAMP activates protein kinase A.
Inactive protein kinase A
Active protein kinase A
4 Protein kinase A phosphorylates inactive designated protein, activating it.
ATP
ADP
Inactive designated protein
(changes shape and function)
P
Active designated protein
5 Active designated protein brings about desired response.
KEY
P = Phosphate
Cellular response


activated adenylyl cyclase
signal molecule
activated α subunit of stimulatory G protein (Gs)
plasma membrane
activated GPCR
GTP
ATP
cyclic AMP
inactive PKA
activated PKA
CYTOSOL
NUCLEUS
nuclear pore
activated PKA
activated, phosphorylated CREB
inactive CREB
CREB-binding protein (CBP)
P
activated target gene
cyclic AMP response element (CRE)
GENE TRANSCRIPTION

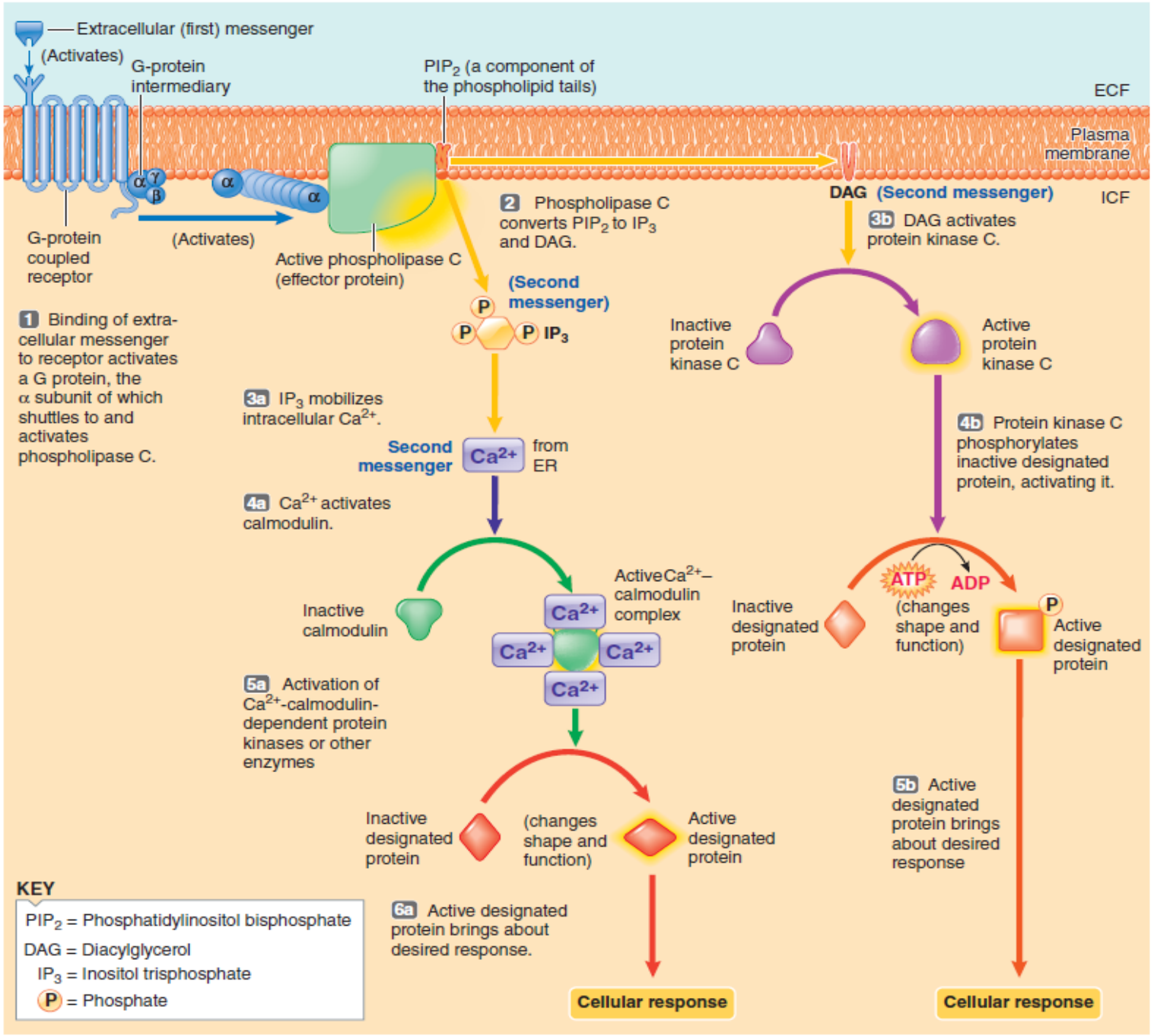
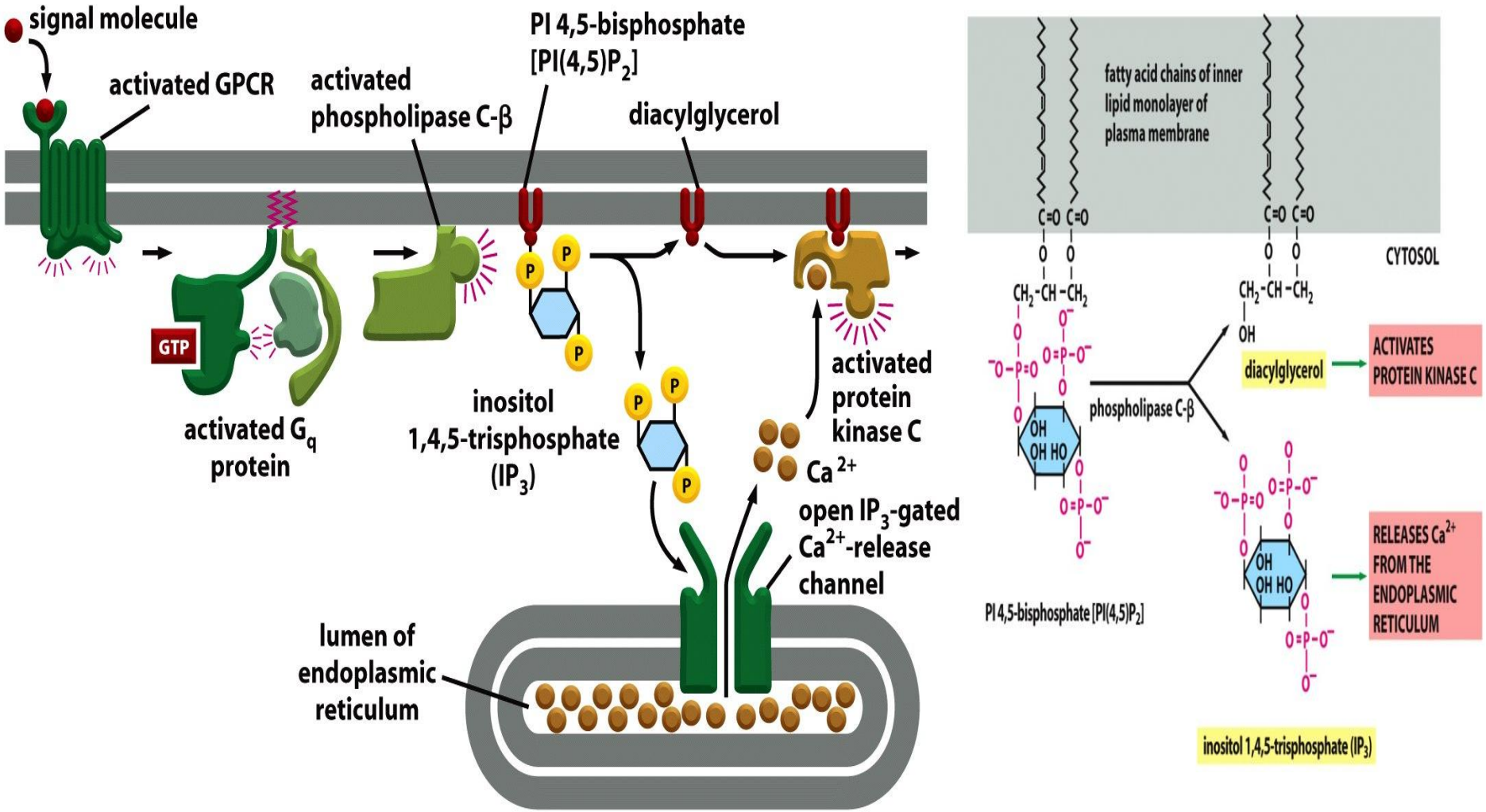


FIGURE 3-20 **Mechanism of action of hydrophilic hormones via concurrent activation of the IP_3/Ca^{2+} second-messenger pathway and the DAG pathway.**


signal molecule
activated GPCR
activated phospholipase C-β
PI 4,5-bisphosphate [PI(4,5)P2]
diacylglycerol
GTP
activated Gq protein
inositol 1,4,5-trisphosphate (IP3)
activated protein kinase C
Ca 2+
open IP3-gated Ca2+-release channel
lumen of endoplasmic reticulum
fatty acid chains of inner lipid monolayer of plasma membrane
CYTOSOL
phospholipase C-β
diacylglycerol
ACTIVATES PROTEIN KINASE C
RELEASES Ca2+ FROM THE ENDOPLASMIC RETICULUM
PI 4,5-bisphosphate [PI(4,5)P2]
inositol 1,4,5-trisphosphate (IP3)

EXTRA NOTES

Enzyme linked receptors

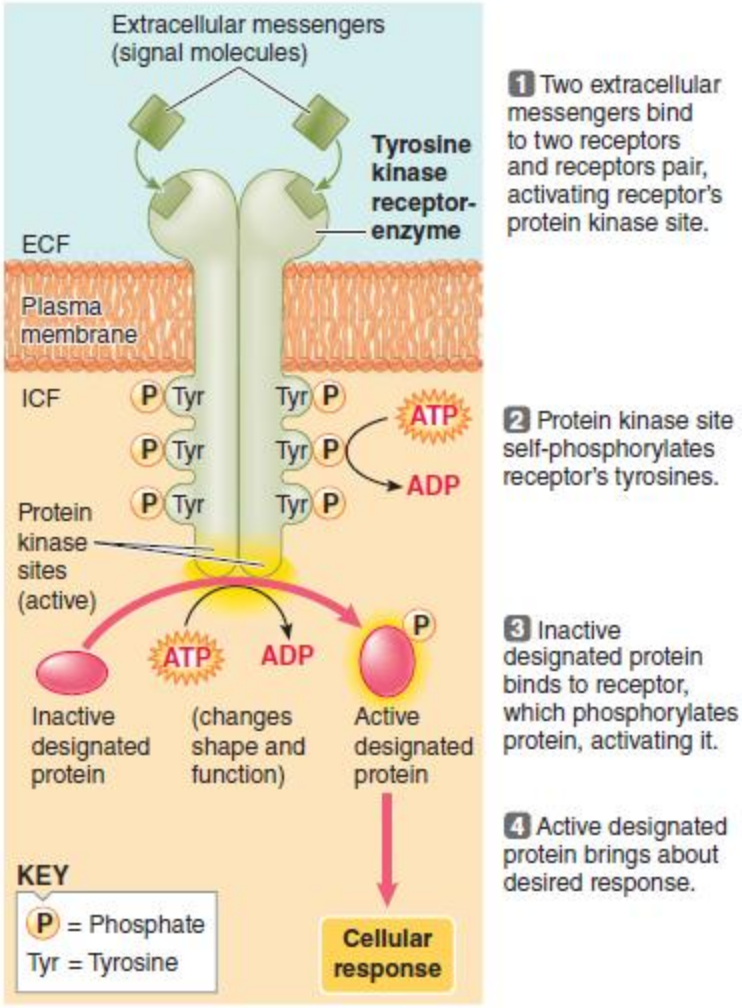
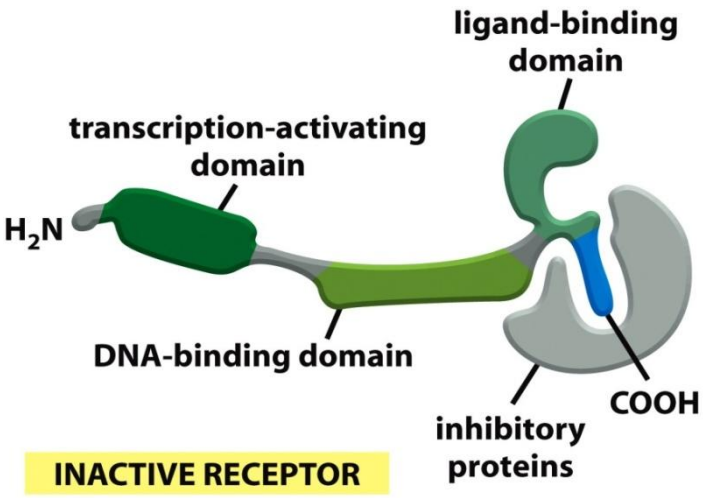
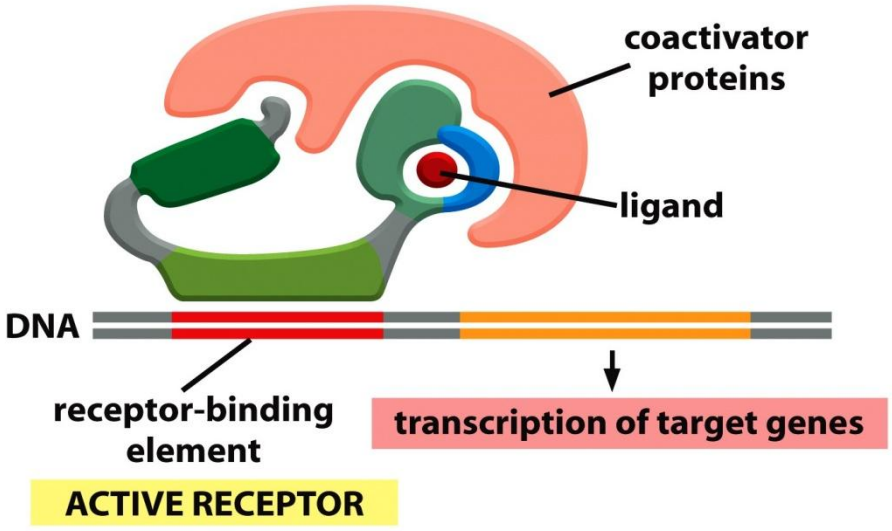


FIGURE 3-18 Tyrosine kinase pathway.

Intracellular Receptors





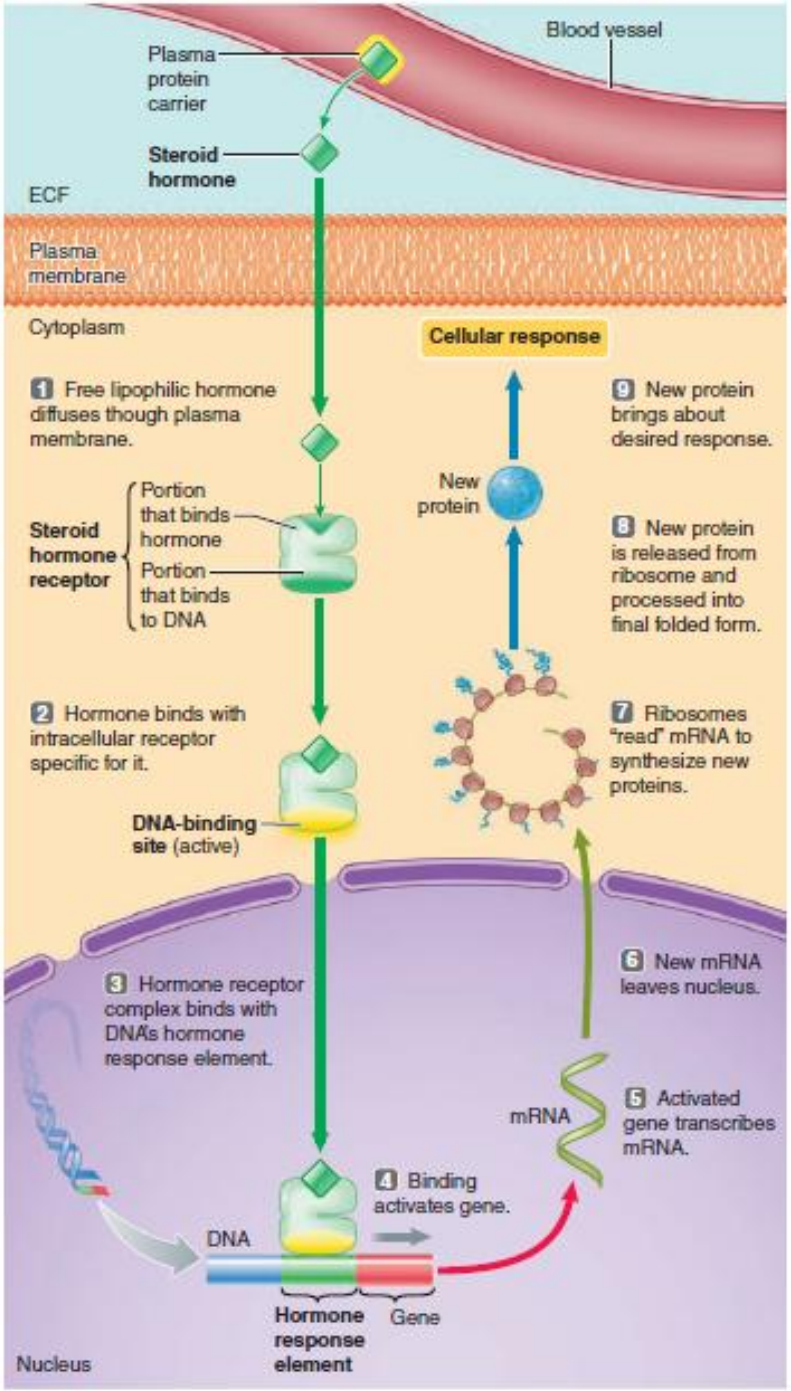
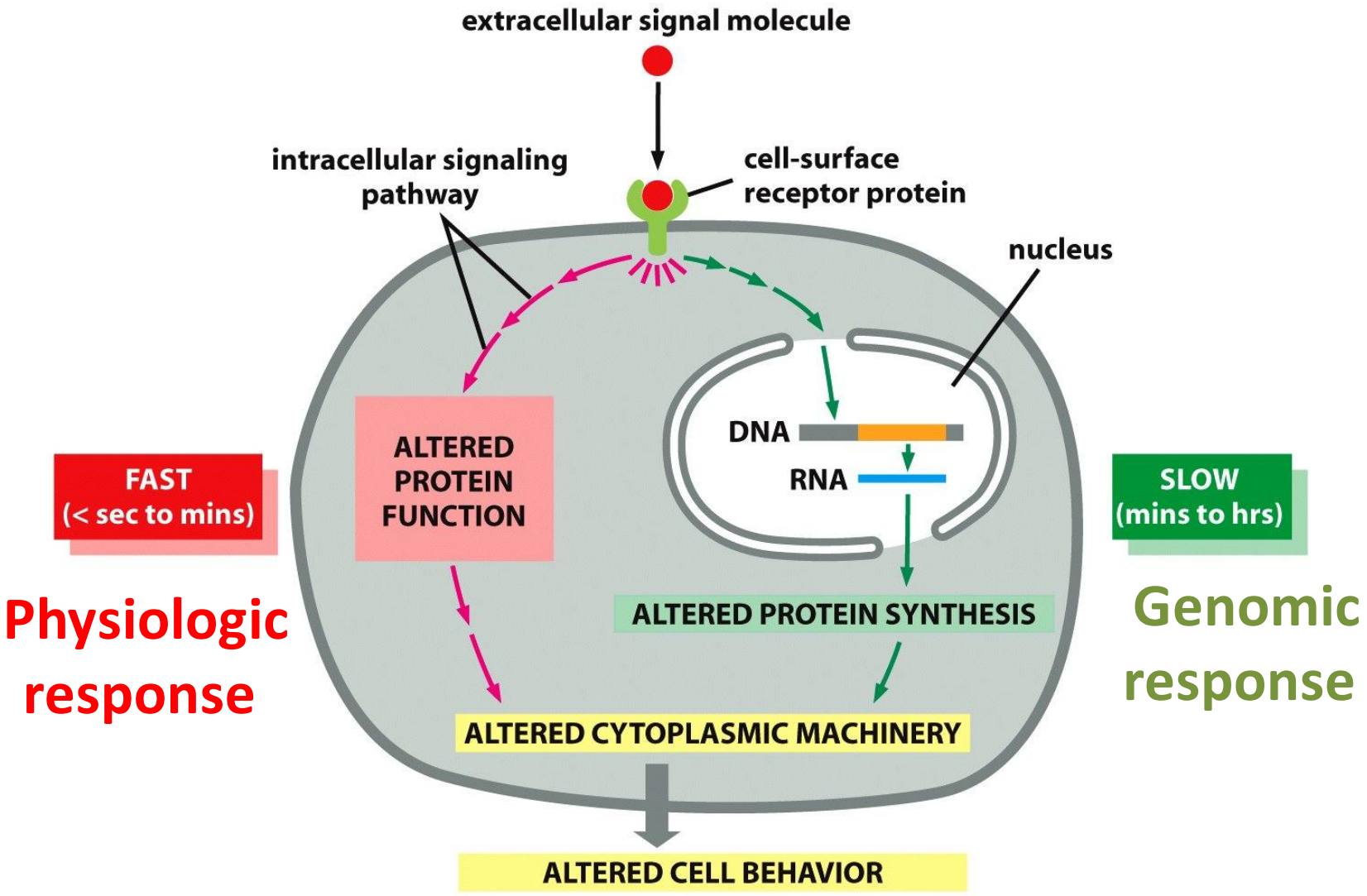


FIGURE 7-4 Mechanism of action of lipophilic hormones.

Types of cellular response



Regulation of Signal transduction