Signal Transduction Lec-1

Alaa Bawaneh, MD. Ph.D

Resource

- Textbook: Guyton and Hall Textbook of Medical Physiology: 14th edition 2021
- Lectures
- Slides

Signaling Overview

A. Definitions

Signaling: **Cell-cell communication via signals.**

Signal transduction: **Process of converting extracellular signals into intra-cellular responses.**

Ligand: **The signaling molecule.**

Receptors: **Bind specific ligands. Transmit signals to intracellular targets.**

Different receptors can respond differently to the same ligand.

B. Components involved in signaling:

Ligands

Receptors

Intracellular Signaling Proteins

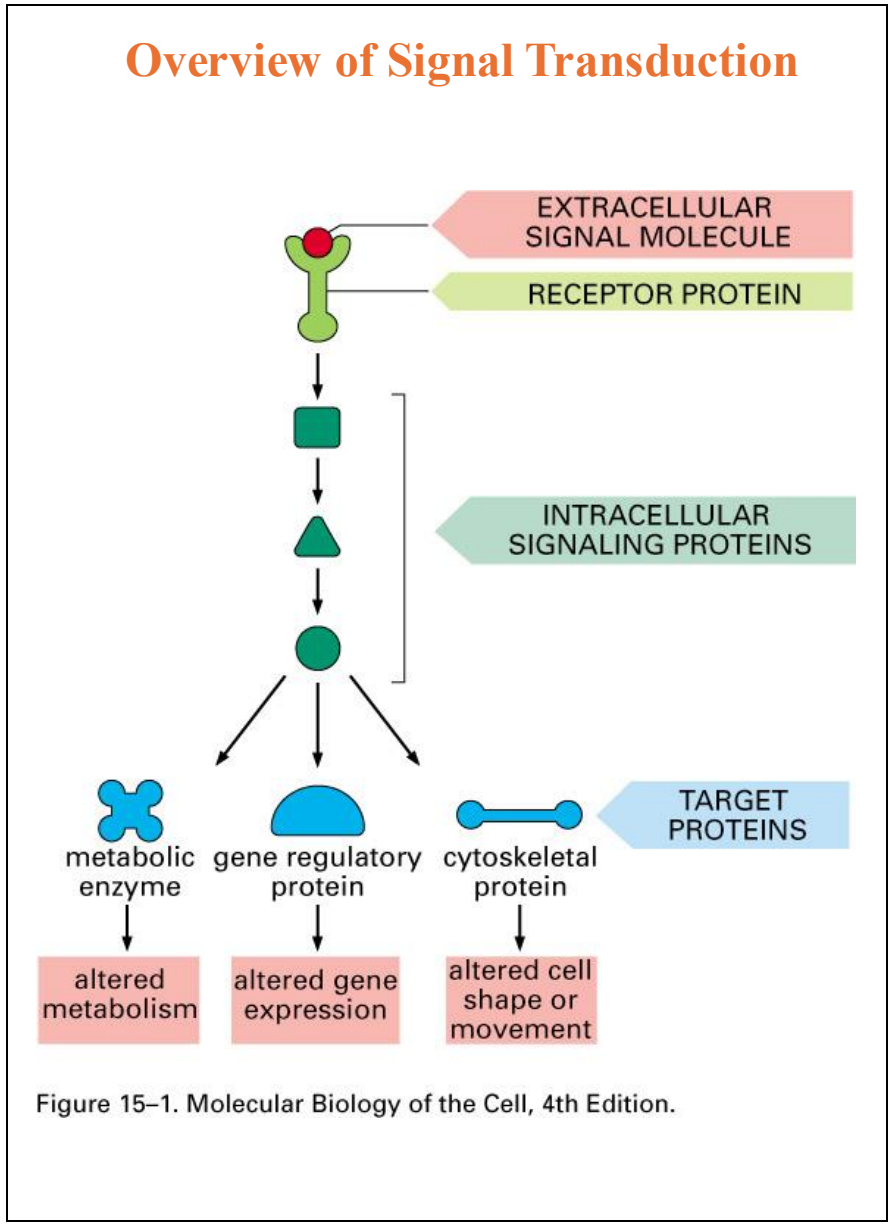
Intermediary Proteins

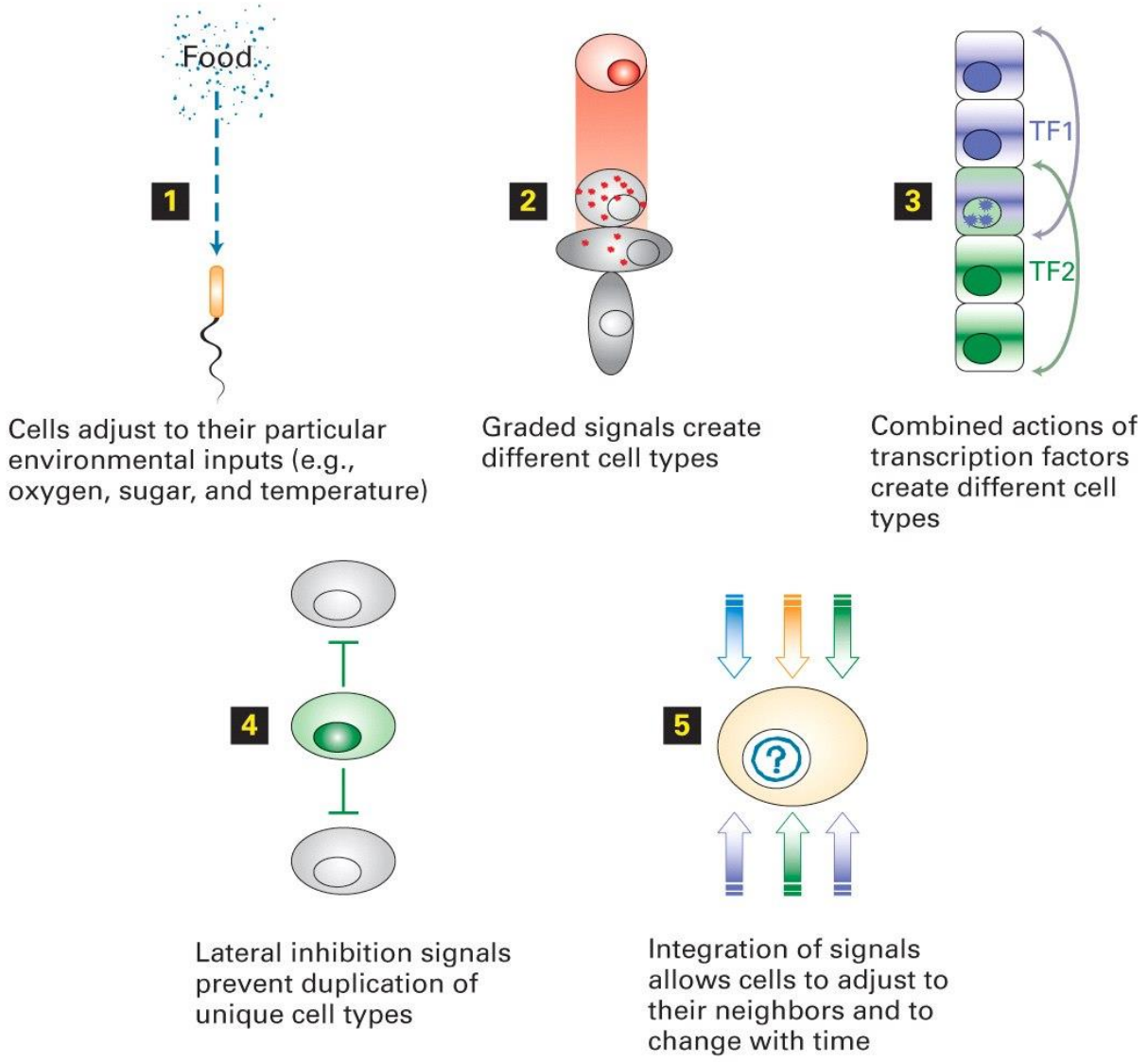
Enzymes

Second Messengers

Target Proteins

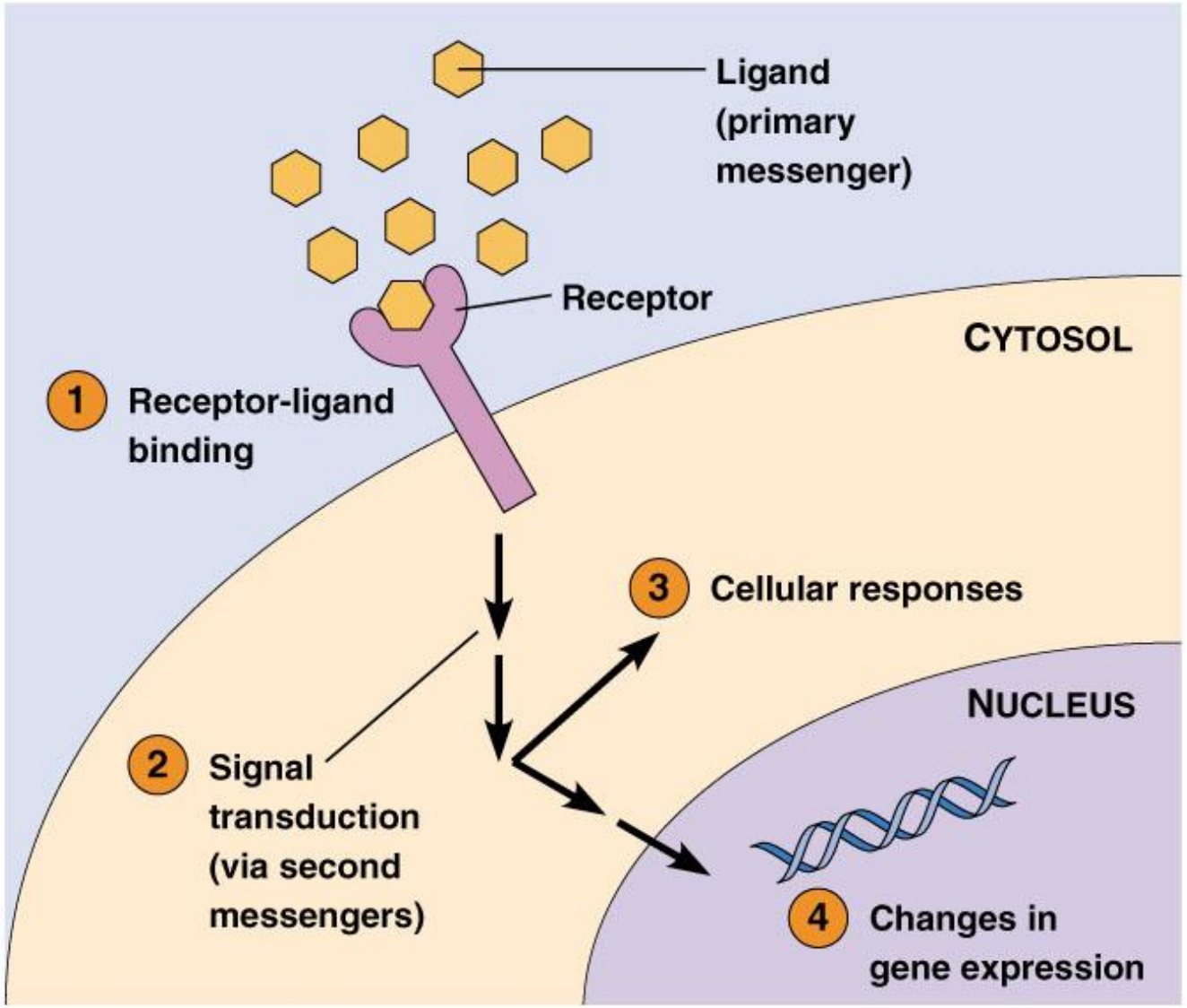
Inactivating Proteins



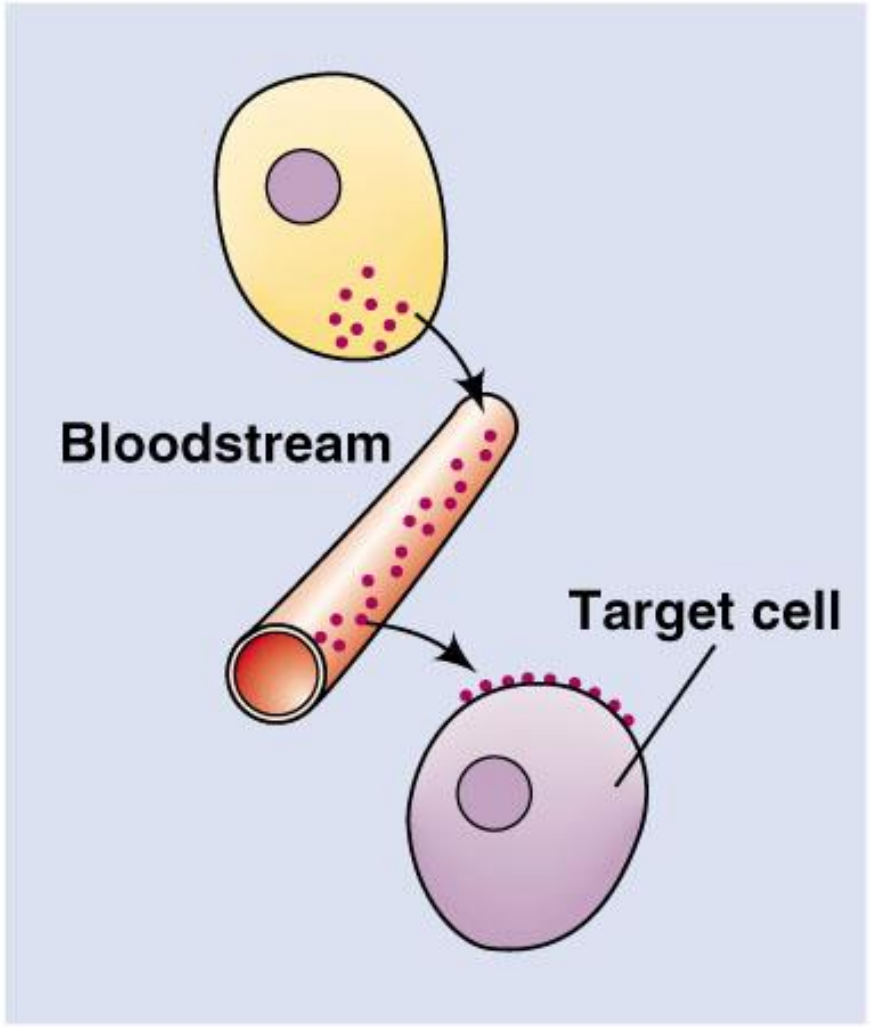


Signaling is responsible for how cells can respond to their environment and how they can differentiate or change over time

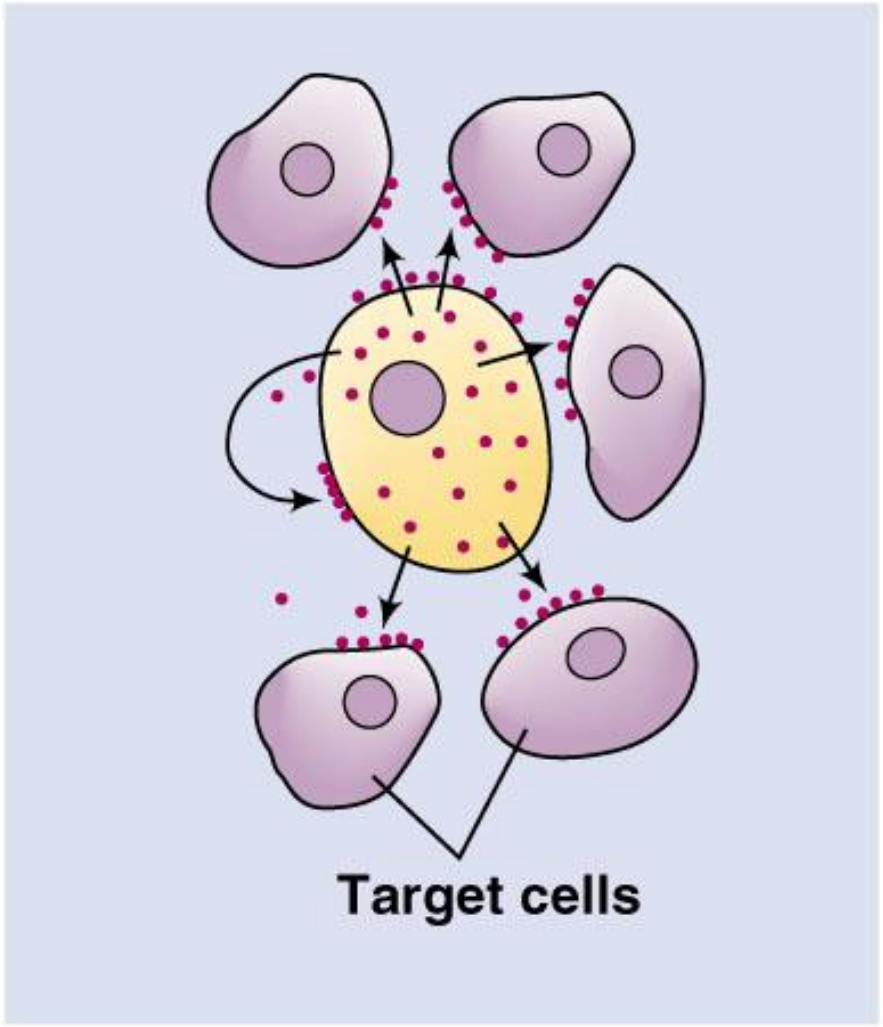
Signals get translated into cellular responses or changes in gene expression



Signals can act locally or at a distance

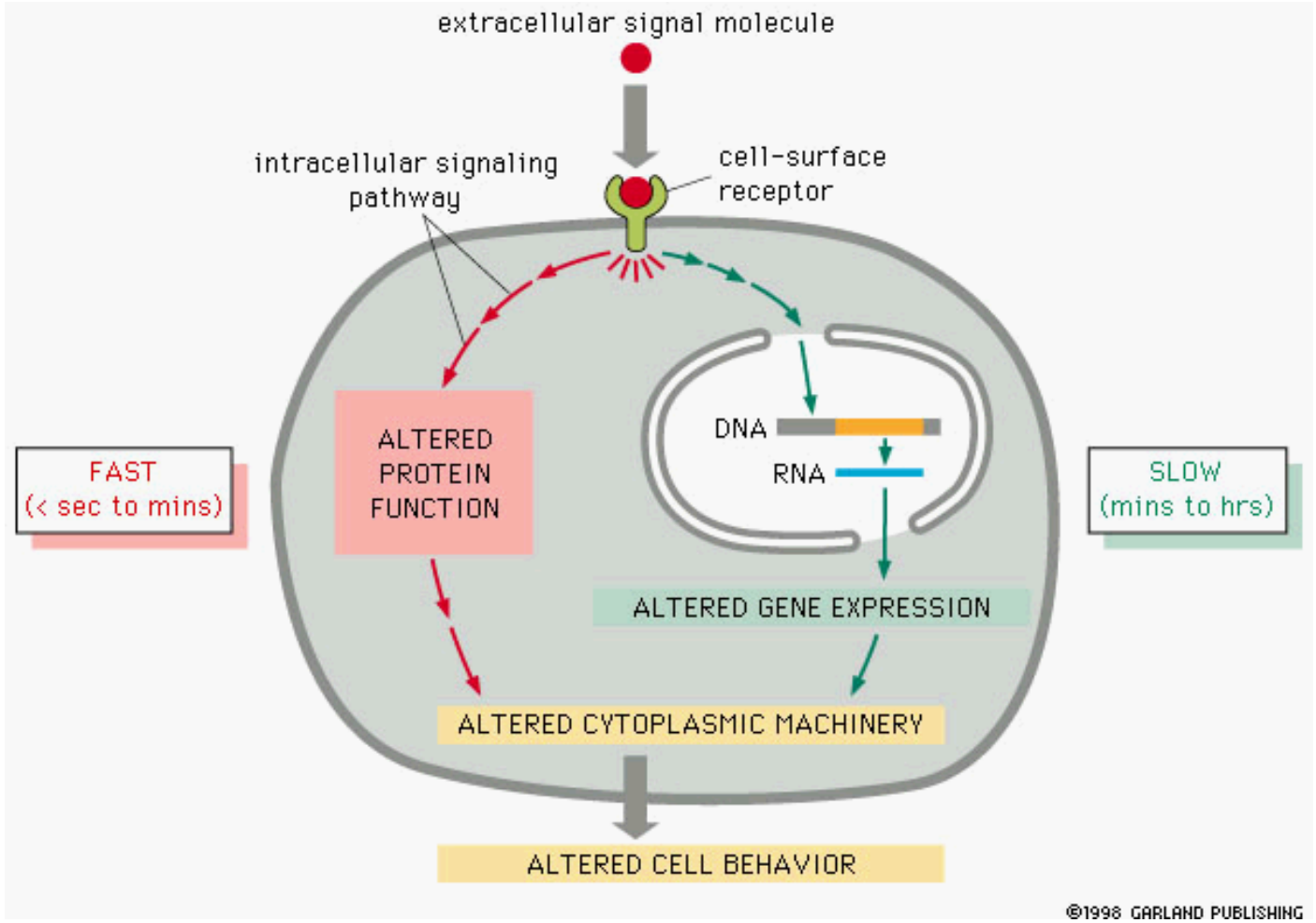


Hormones

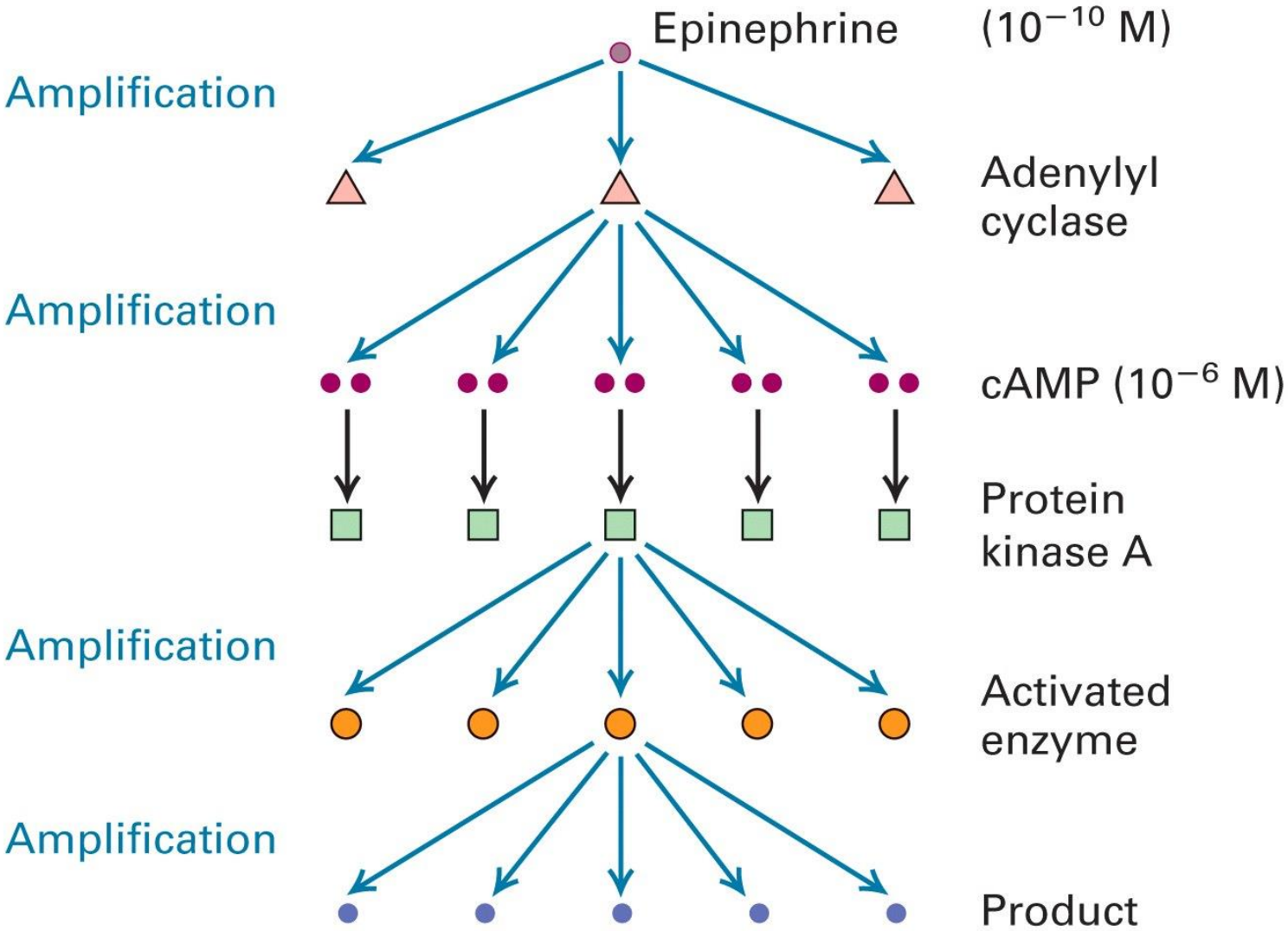


Local mediators

Responses can be fast or slow



Signals are amplified



Signaling Overview

C. Types of signaling

i. Contact-dependent - via proteins in the PM

ii. Via Secreted Signals:

a. Autocrine - via growth factors, cell that releases the signal is also the target.

b. Paracrine - via neurotransmitters and cytokines, action on adjacent target cells.

c. Endocrine - via hormones, action on distant target cells.

d. Synaptic - via neurotransmitters, action on post-synaptic cell in response to electrical stimuli

2. Types of Signaling Ligands:

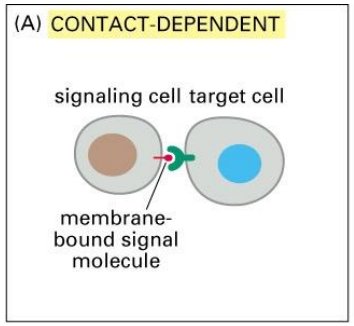
A. Ligands that bind to cell-surface receptors:

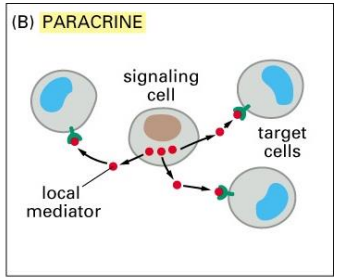
1. **Neurotransmitters (NT), i.e. norepinephrine, histamine - hydrophilic (charged, polar)**
2. **Peptide hormones (P), i.e. insulin - can't cross membrane**
3. **Growth factors (GF), i.e. NGF, EGF, PDGF**
4. **Lipophilic signaling molecules, i.e. prostaglandins**

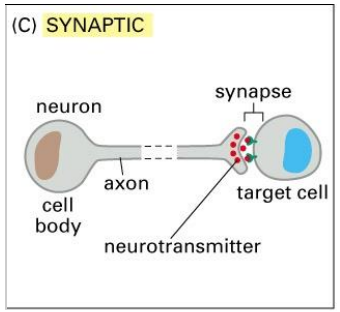
B. Ligands that bind to intracellular receptors:

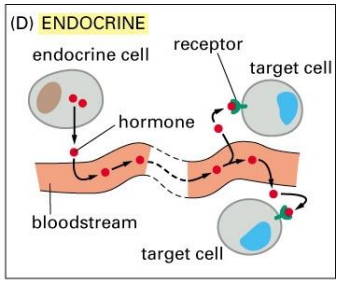
lipid soluble hormones that diffuse across the plasma membrane and interact with receptors in the cytosol or nucleus. i.e. steroids, thyroxine, retinoic acid, nitric oxide.

Types of Signaling





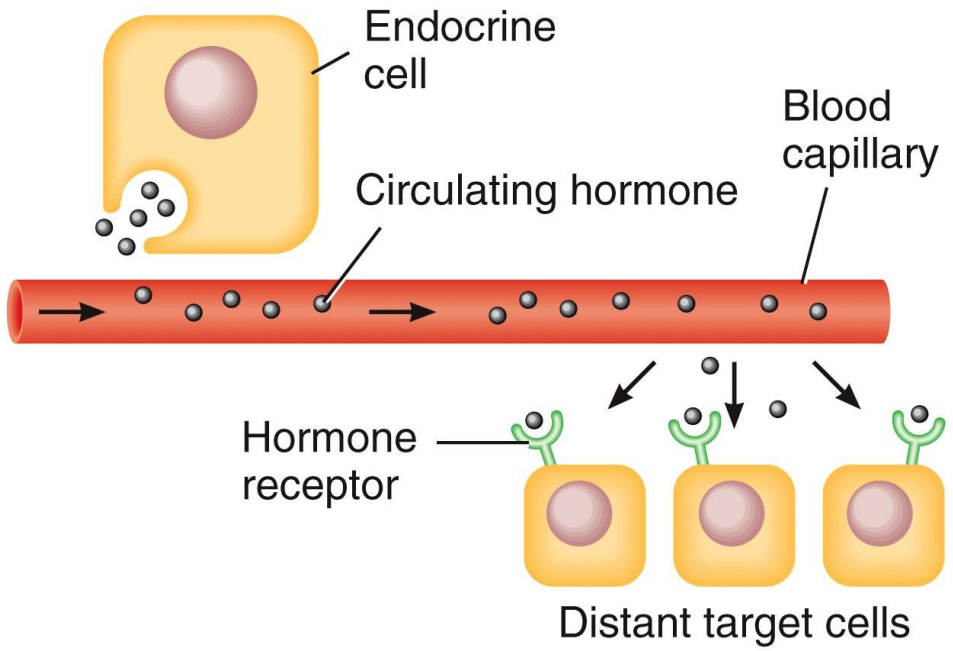




Types of Signaling

- **Endocrine**

are secreted into interstitial fluid and then absorbed into the bloodstream to be carried systemically to any cell that displays the appropriate type of receptor.

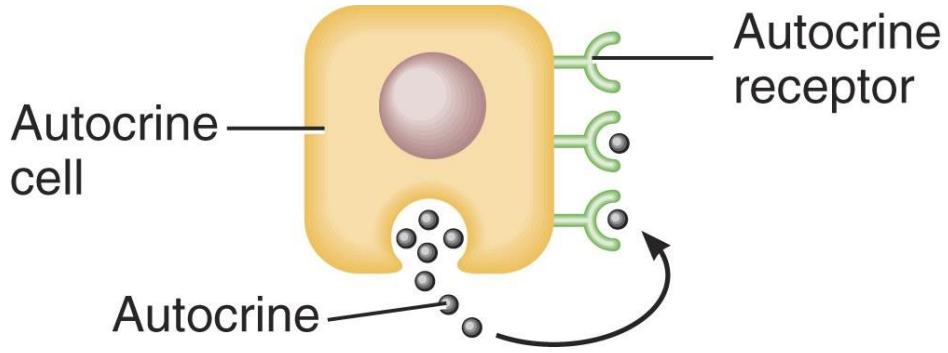


(a) Circulating hormones

Types of Signaling

- **Autocrine**

are local hormones that are secreted, and bind to the same cell.



- **E.g.** Interleukin- 2 (IL-2),

  which is released by helper

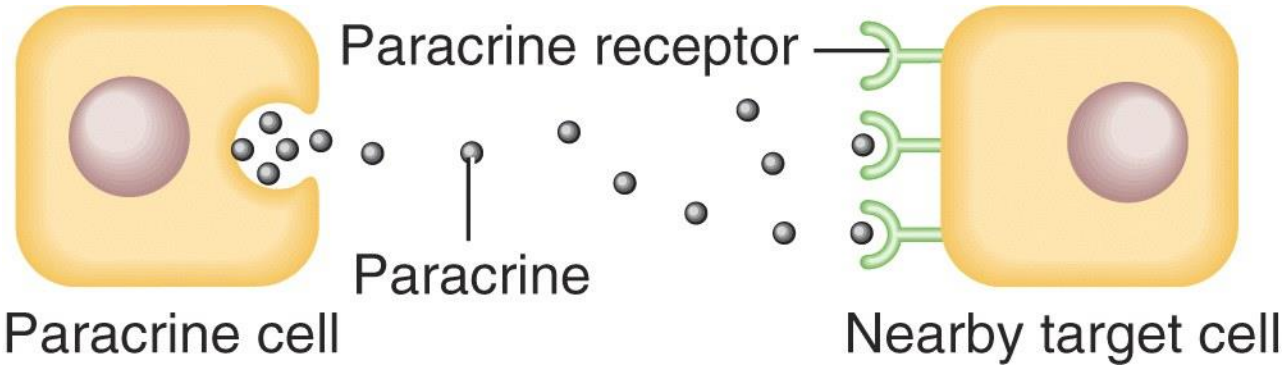
  T cells.

Types of Signaling

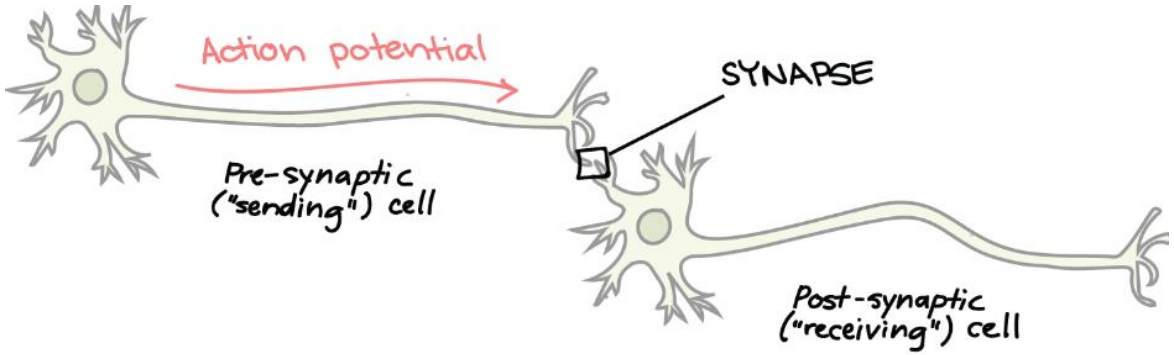
- **Paracrine**

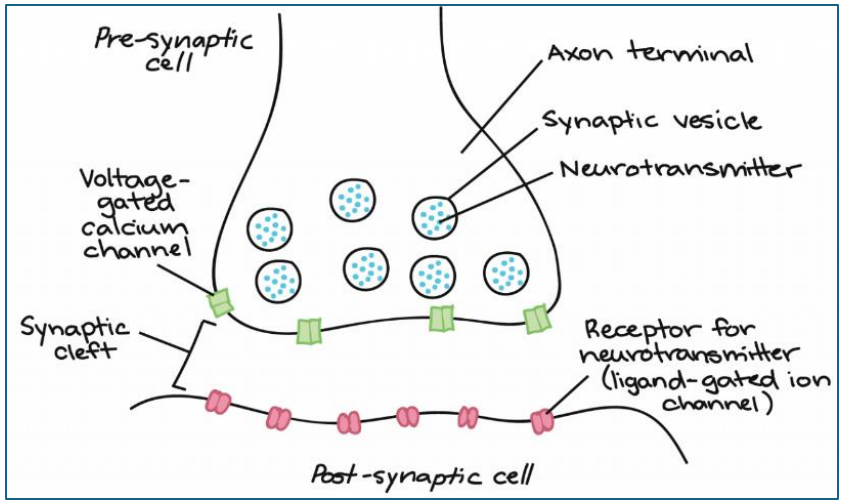
are local hormones that are secreted into interstitial fluid and act on nearby cells

- **E.g. nitric oxide (NO).**



Chemical Transmission at The Synapse





Chemical Classes of Hormones

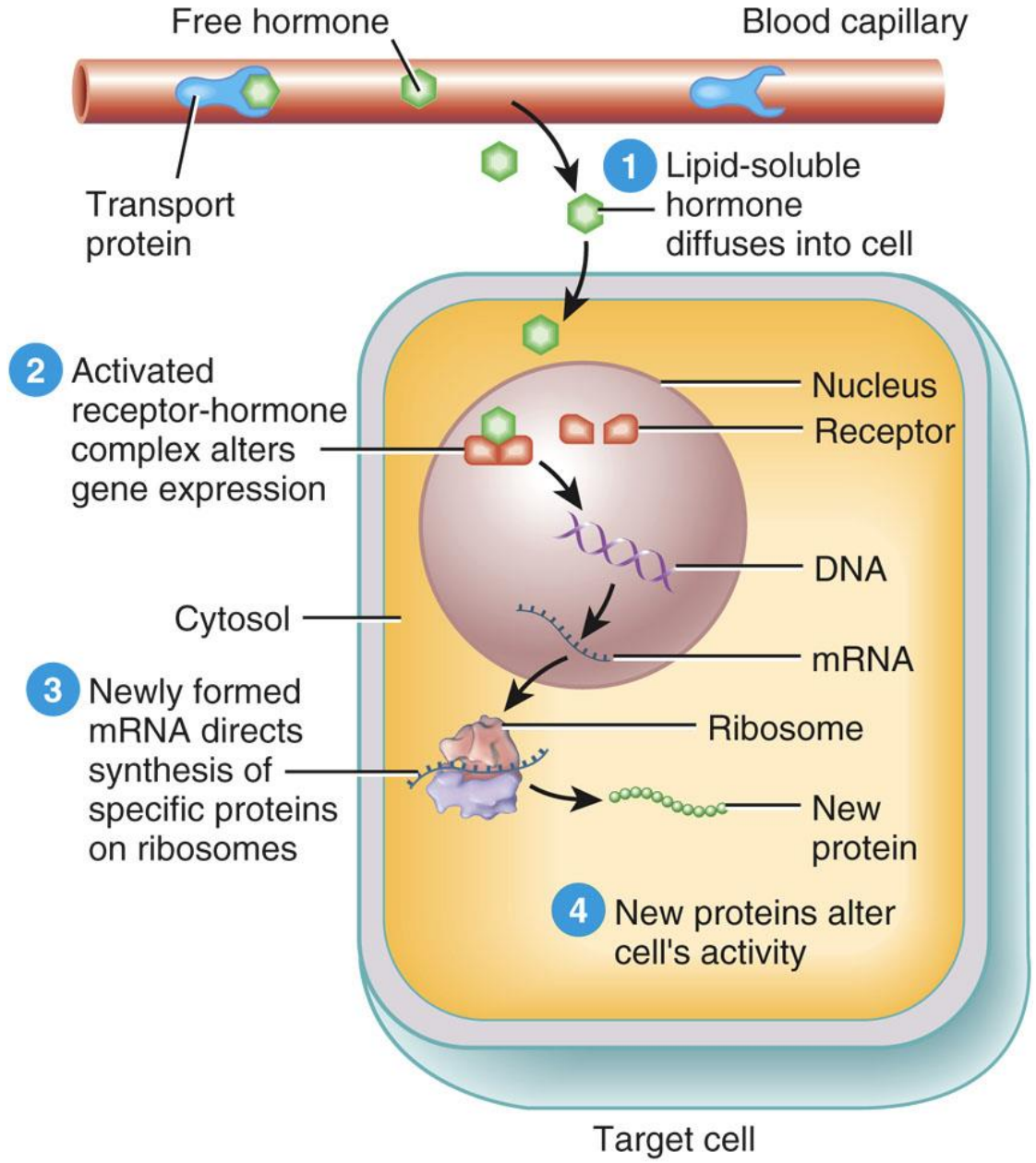
- Hormones can be divided into two broad **chemical classes.**
- **Lipid soluble hormones**
- **Water soluble hormones**

Lipid soluble hormones (Lipophilic)

- Consist of steroid hormones, thyroid hormones, and the gas nitric oxide

  - Steroid hormones are derived from cholesterol
  - Thyroid hormones (T3 and T4) are synthesized by attaching iodine to the amino acid tyrosine.
  - The gas nitric oxide (NO).

- **Lipid soluble hormones** require a carrier protein for transport in the watery environment of the blood
- Once they arrive at their destination, however, they are able to freely pass through the plasma membrane to bind to receptors located in the cytoplasm or the nucleus of the target cell

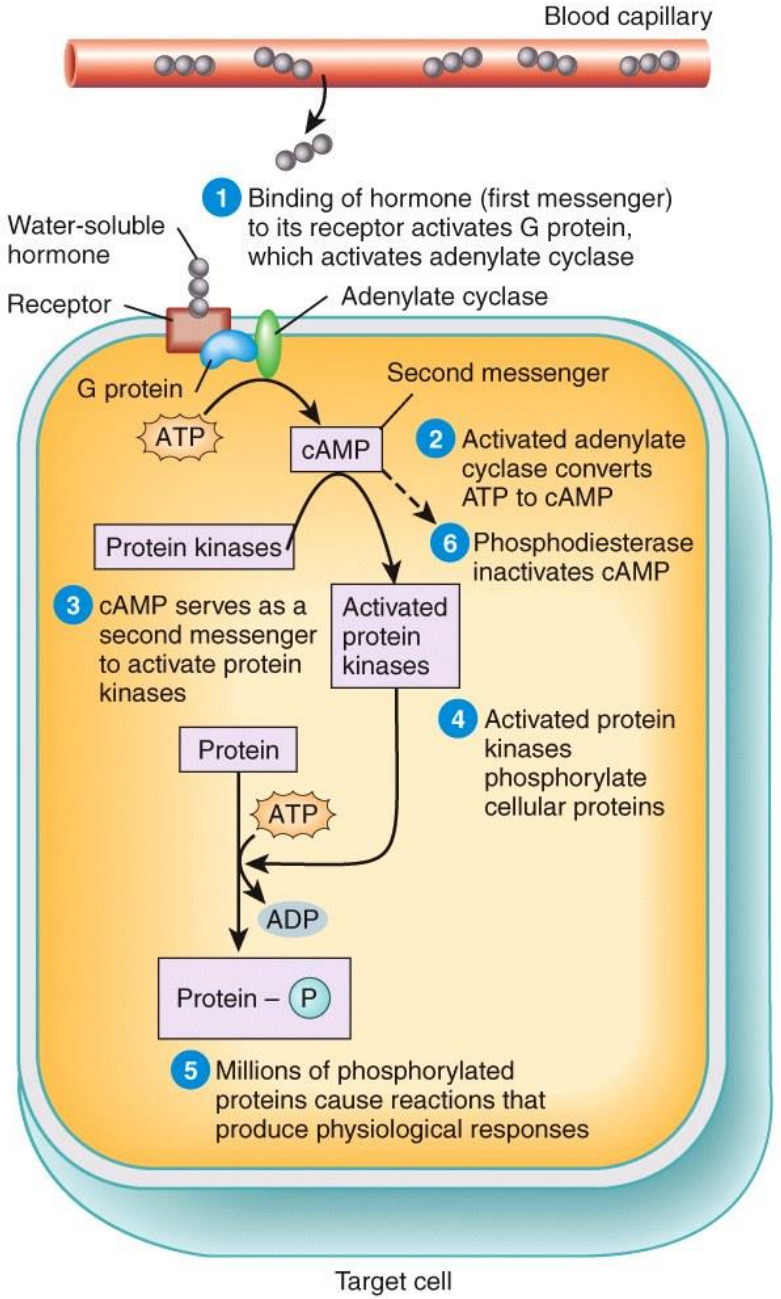


Water soluble hormones (Hydrophilic)

- ✓ Peptide hormones and protein hormones.
- ✓ local hormones derived from the arachidonic acid on our cell membranes called eicosanoids
  - The two major types of eicosanoids are prostaglandins and leukotrienes – both play a role in mediating the inflammatory response

- **Water soluble hormones** are easy to transport in the watery blood. The plasma membrane of target cells, however, is impermeable to them.

- The first messenger (the hormone) then causes production of a second messenger (cAMP) inside the cell, where specific hormone-stimulated responses take place.



Chemical classification of hormones

Table 10-4 Chemical Classification and Function of Hormones

Chemical Classification	Examples	Regulated Function
Endocrine Hormones		
Amino acid derivatives	Epinephrine (adrenaline) and norepinephrine (both derived from tyrosine)	Stress responses: regulation of heart rate and blood pressure; release of glucose and fatty acids from storage sites
	Thyroxine (derived from tyrosine)	Regulation of metabolic rate
Peptides	Antidiuretic hormone (vasopressin)	Regulation of body water and blood pressure
	Hypothalamic hormones (releasing factors)	Regulation of tropic hormone release from pituitary gland
Proteins	Anterior pituitary hormones	Regulation of other endocrine systems
Steroids	Sex hormones (androgens and estrogens)	Development and control of reproductive capacity
	Corticosteroids	Stress responses; control of blood electrolytes
Paracrine Hormones		
Amino acid derivative	Histamine	Local responses to stress and injury
Arachidonic acid derivatives	Prostaglandins	Local responses to stress and injury

Peptide & Protein Hormones

Gland/Tissue	Hormones
Hypothalamus	■ TRH, GnRH, CRH GHRH, Somatostatin,
Anterior pituitary	■ ACTH, TSH, FSH, LH, PRL, GH
Posterior pituitary	■ Oxytocin, ADH
Thyroid	■ Calcitonin
Pancreas	■ Insulin,Glucagon, Somatostatin
Liver	■ Somatomedin C (IGF-1)
Parathyroid	■ PTH

Gland/Tissue	Hormones
Placenta	■ HCG, HCS or HPL
Kidney	■ Renin (enzyme) ■ Ang II (peptide)
Heart	■ ANP
G.I. tract	■ Gastrin, CCK, Secretin, GIP, Somatostatin
Adipocyte	■ Leptin

Steroid Hormones

Gland/Tissue	Hormones
Adrenal Cortex	■ Cortisol, Aldosterone, Androgens
Testes	■ Testosterone
Ovaries	■ Estrogens, Progesterone
Corpus Luteum	■ Estrogens, Progesterone
Placenta	■ Estrogens, Progesterone
Kidney	■ 1,25-Dihydroxycholecalciferol (calcitriol)

Amine Hormones

Gland/Tissue	Hormones
Hypothalamus	■ Dopamine
Thyroid	■ T_3, T_4
Adrenal medulla	■ Epinephrine and Norepinephrine (NE, EPI)

Chemical classes of hormones

- Lipid-soluble hormones- use transport proteins in the **plasma**
  - Steroid: Lipids derived from cholesterol.
    - Are lipophilic hormones.
      - Testosterone.
      - Estradiol.
      - Cortisol.
      - Progesterone.
  - Thyroid (amine but lipid soluble)
  - Nitric oxide (NO)

Chemical classes of hormones

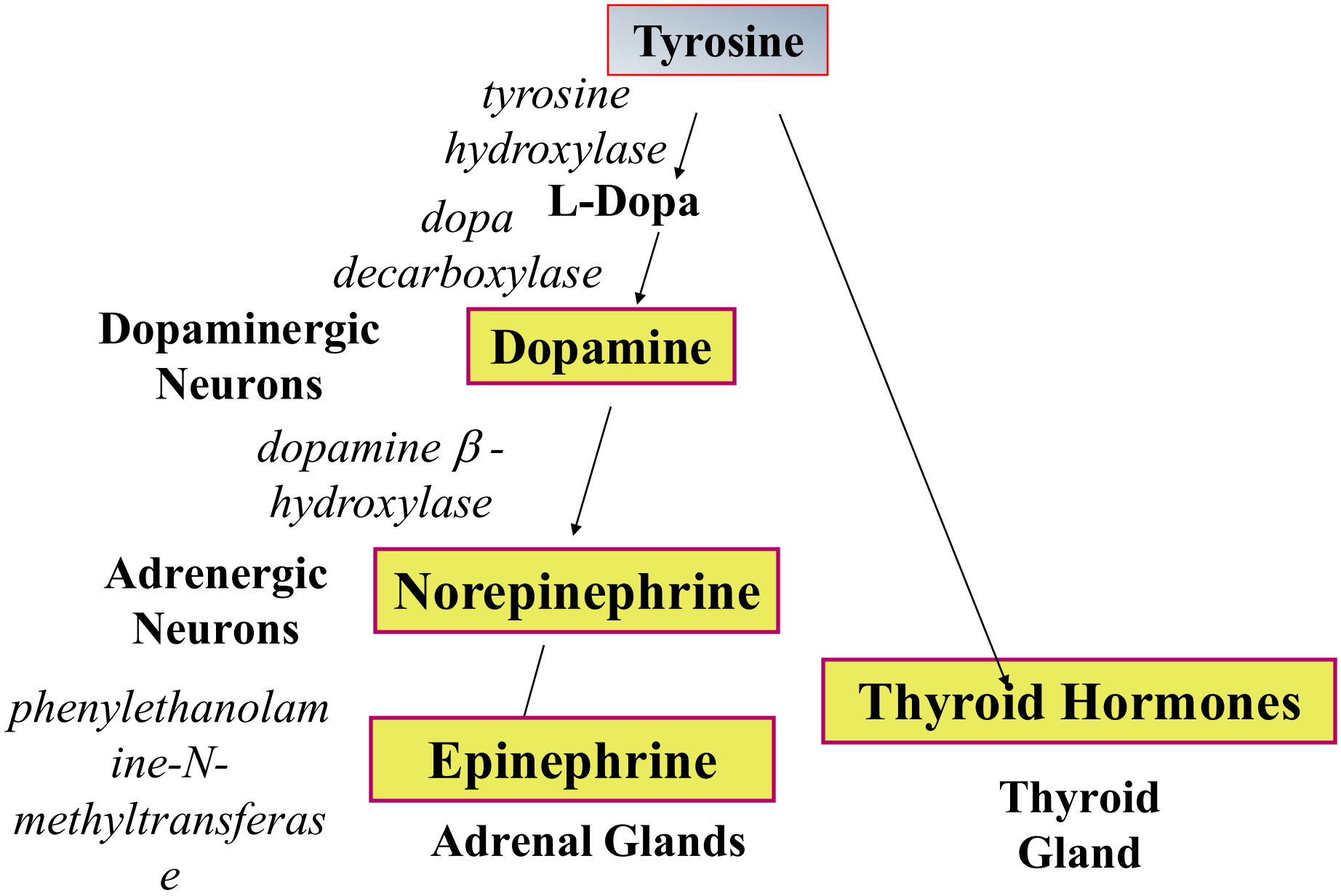
- Water-soluble – circulate in "free" form in the plasma
  - Amines:
    - Hormones derived from tyrosine and tryptophan.
  - Polypeptides and proteins:
    - Polypeptides:
      - Chains of < 100 amino acids in length.
        - ADH.
    - Protein hormones:
      - Polypeptide chains with > 100 amino acids.
      - Growth hormone.
  - Eicosanoid (prostaglandins) derived from arachidonic acid (20 carbon 4 double bonds)

Chemical Classification of Hormones

- Glycoproteins:
  - Long polypeptides (>100) bound to 1 or more carbohydrate (CHO) groups.
    - FSH and LH, TSH and hCG (human chorionic gonadotropin)

      They have α and β subunits (α is common and β is specific)
- Hormones can also be divided into:
  - Polar:
    - H_20 soluble.
  - Nonpolar (lipophilic):
    - H_20 insoluble.
      - Can gain entry into target cells.
      - Steroid hormones and T_4 (thyrxine –tetraiodothyronine))

Synthesis of Amine Hormones



Prohormones and Prehormones

- Prohormone:
  - Precursor is a longer chained polypeptide that is cut and spliced together to make the hormone.
    - Proinsulin – gives insulin
- Preprohormone:
  - Prohormone derived from larger precursor molecule.
    - Preproinsulin.
- Prehormone:
  - Molecules secreted by endocrine glands that are inactive until changed into hormones by target cells.
    - T_4 converted to T_3 (tri-iodothyronin).

Hormone Activity

- Hormones affect only specific target tissues with specific receptors
- Receptors are dynamic and constantly synthesized and broken down
  - Down-regulation- decrease in receptor number or response
  - Up-regulation- increase in receptor number or activity

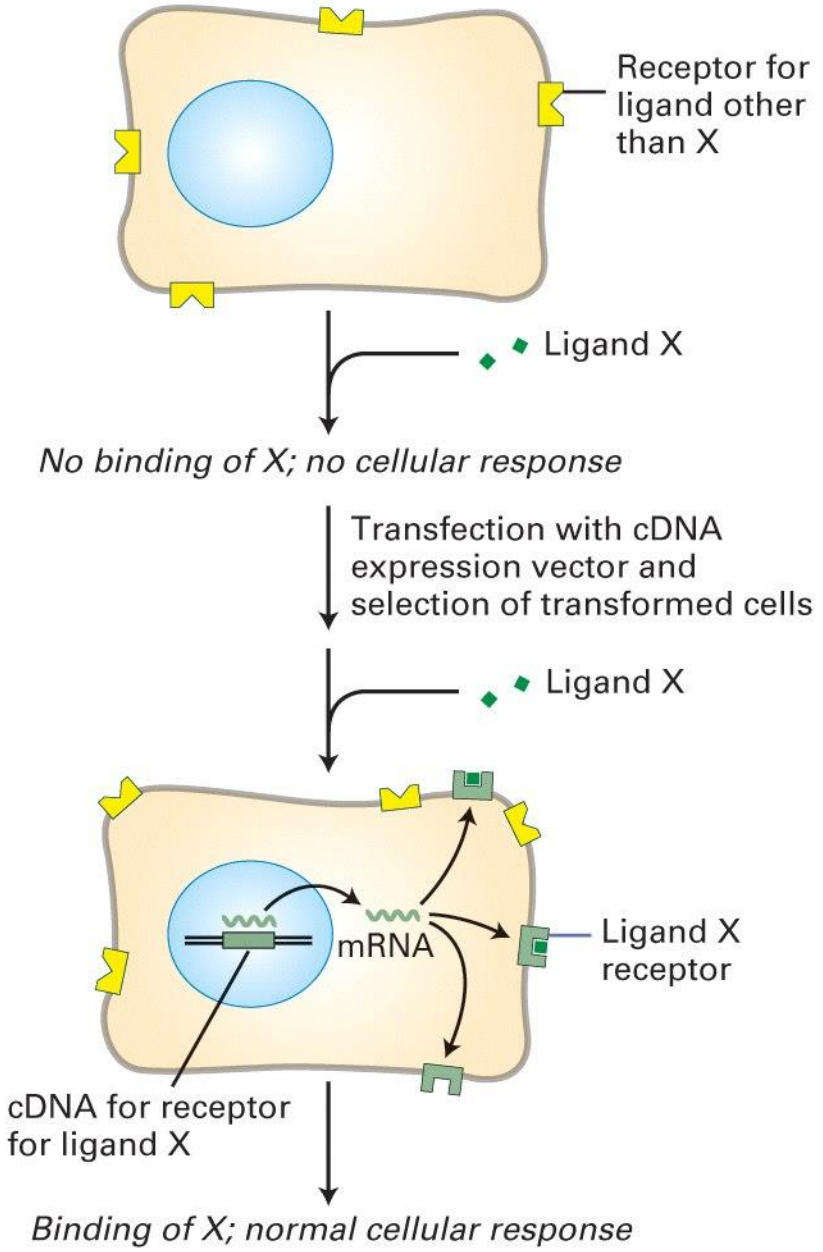
Receptor

Receptors are specific membrane proteins, which are able to recognize and bind to corresponding ligand molecules, become activated, and transduce signal to next signaling molecules.

Glycoprotein or Lipoprotein

Receptors determine response

No receptor - no response



Ligand

A small molecule that binds specifically to a larger one; for example, a hormone is the ligand for its specific protein receptor.

Receptors and Ligands

- **Specificity**: The "specificity" of a ligand for a receptor is a description of how favorable the binding of the ligand for the receptor is compared with its possible binding to other types of receptors that may also be present.

- **Affinity**: "Affinity" simply refers to how strong the binding is (as judged by K association or K dissociation and ΔGo). "High affinity" refers to very strong binding (large negative ΔGo and a very small Kd). The association or dissociation constant is often referred to as the "affinity" or "binding" constant.

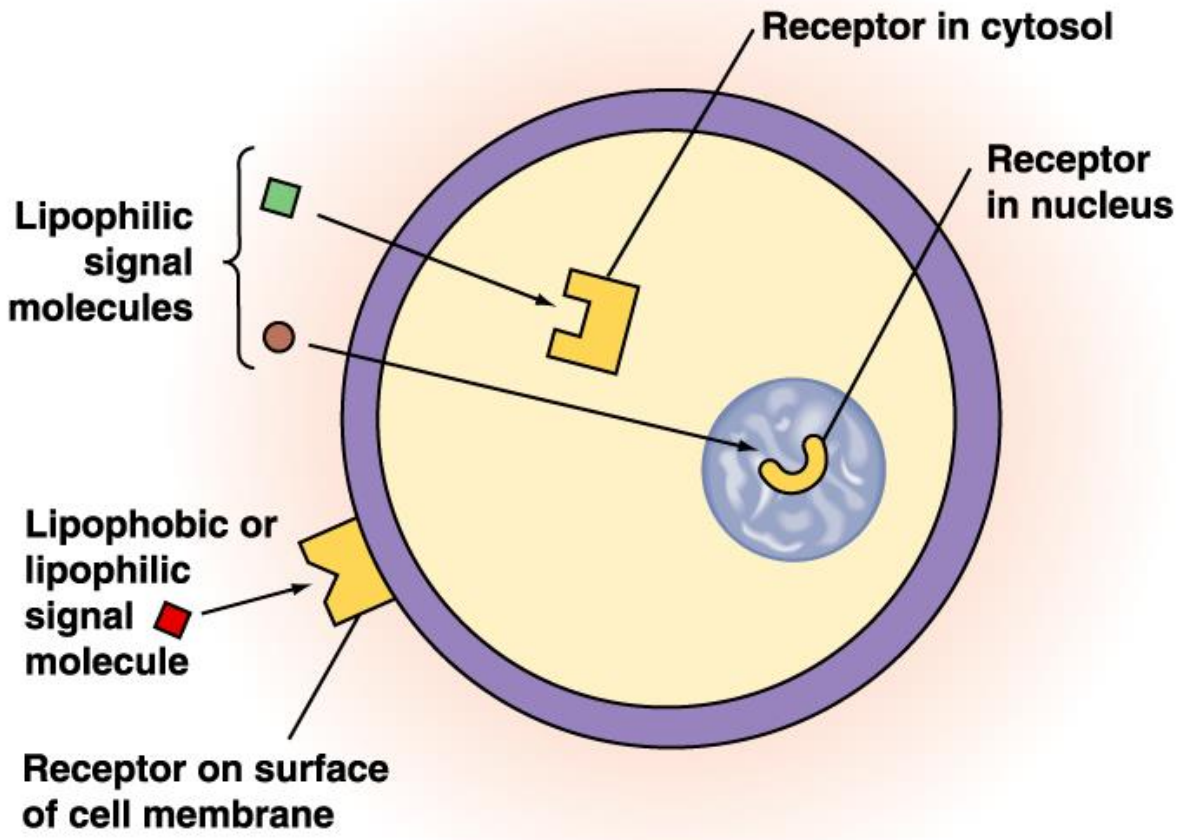
- Membrane receptors

  Membrane Glycoprotein

- Intracellular receptors

  Cytosol or nuclei

  DNA binding protein

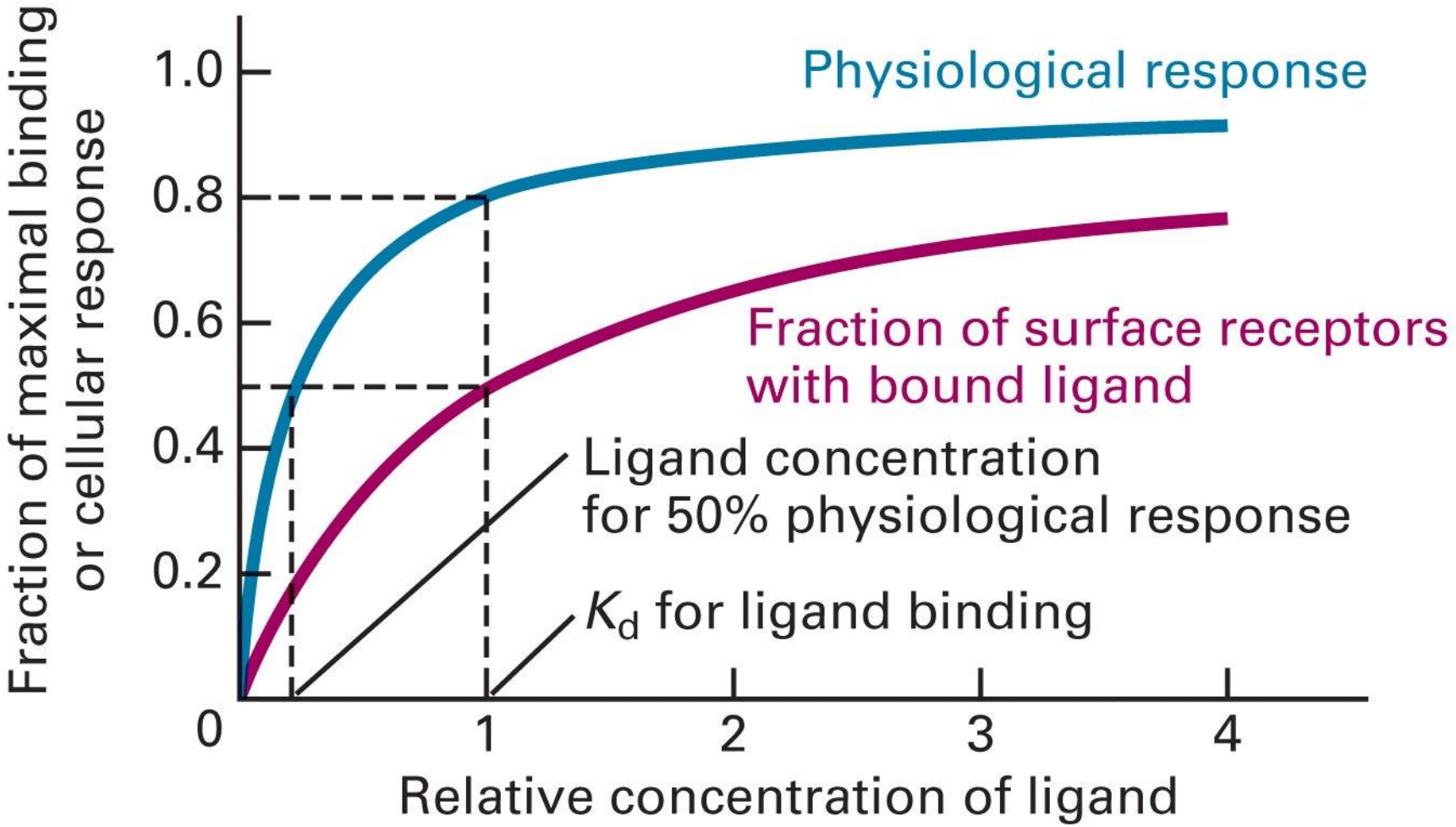


Mechanisms of Hormone Action

- Response depends on both hormone and target cell
- Lipid-soluble hormones bind to receptors inside target cells
- Water-soluble hormones bind to receptors on the plasma membrane
  - Activates second messenger system
  - Amplification of original small signal
- Responsiveness of target cell depends on
  - Hormone's concentration
  - Abundance of target cell receptors

Effects of hormone concentration on Tissue Response

- [Hormone] in blood reflects the rate of secretion.
- Half-life:
  - Time required for the blood [hormone] to be reduced to ½ reference level.
    - Minutes to days.
- Affinity of receptors to ligands, Kd
- Normal tissue responses are produced only when [hormone] are present within physiological range.
- Varying [hormone] within normal, physiological range can affect the responsiveness of target cells.



Not all of the receptor needs to be bound to induce a response

Effects of [Hormone] on Tissue Response

- Priming effect (upregulation):
  - Increase number of receptors formed on target cells in response to particular hormone.
  - Greater response by the target cell.
- Desensitization (downregulation):
  - Prolonged exposure to high [polypeptide hormone].
    - Subsequent exposure to the same [hormone] produces less response.
      - Decrease in number of receptors on target cells.
        - Insulin in adipose cells.
  - Pulsatile secretion may prevent downregulation.

Signaling Overview

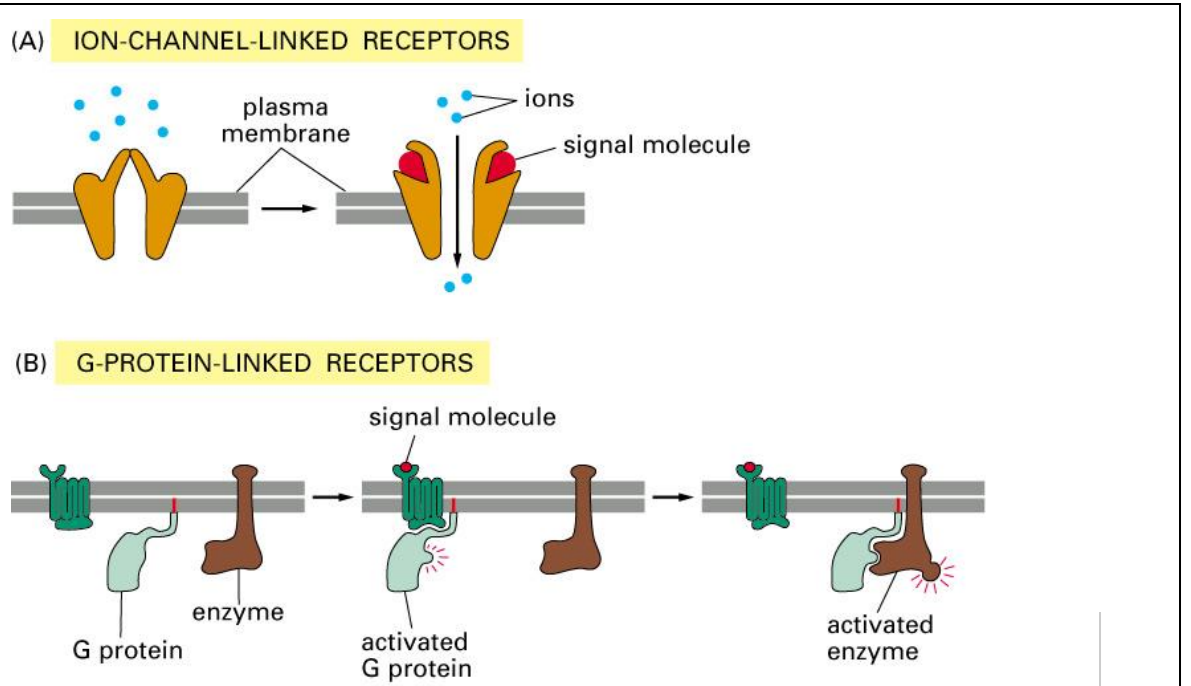
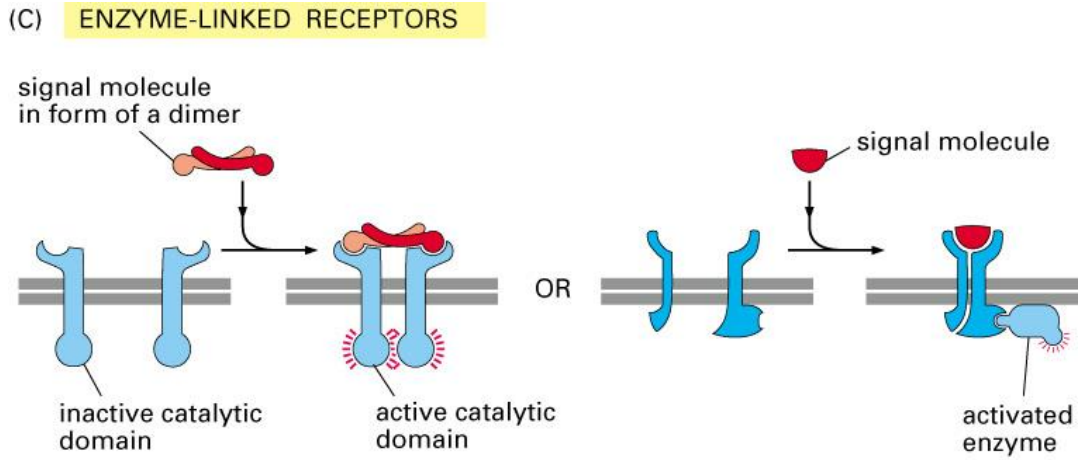


Figure 15–15 part 1 of 2. Molecular Biology of the Cell, 4th Edition.



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