بسم الله الرحمن الرحيم

Physiology | Lecture 5

Signal Transduction

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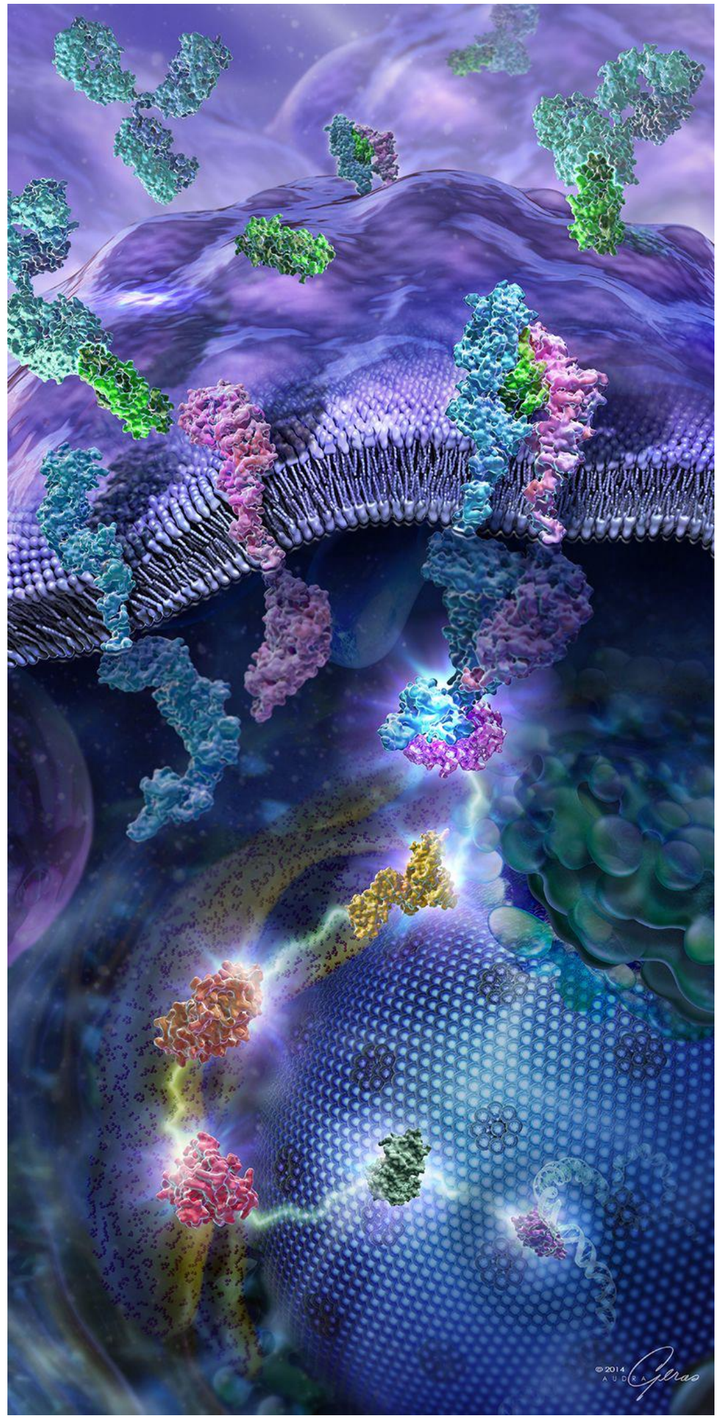
Signal Transduction
Lec-1

Resource

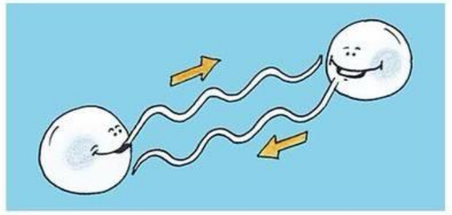
Textbook: Guyton and Hall Textbook of Medical Physiology: 14th edition 2021

Lectures

Slides



Signaling Overview



CELL TO CELL COMMUNICATION

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

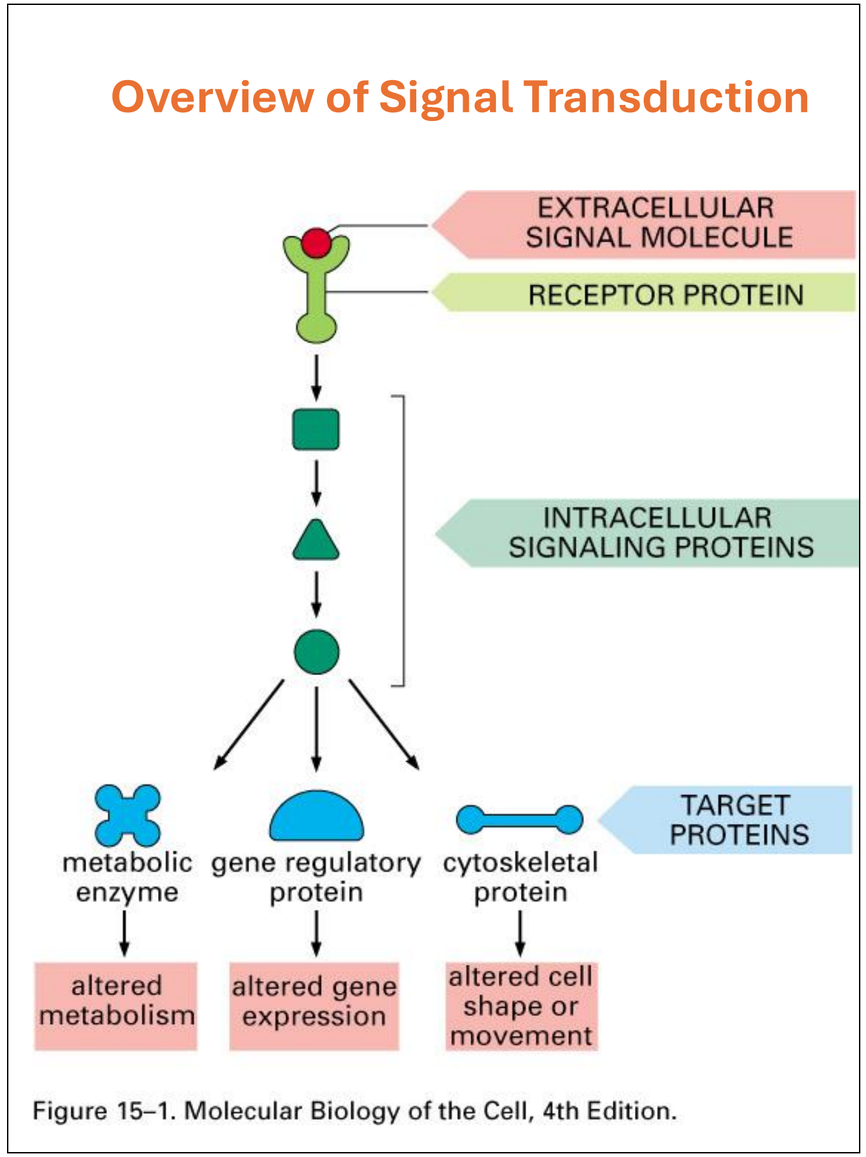


Figure 15–1. Molecular Biology of the Cell, 4th Edition.

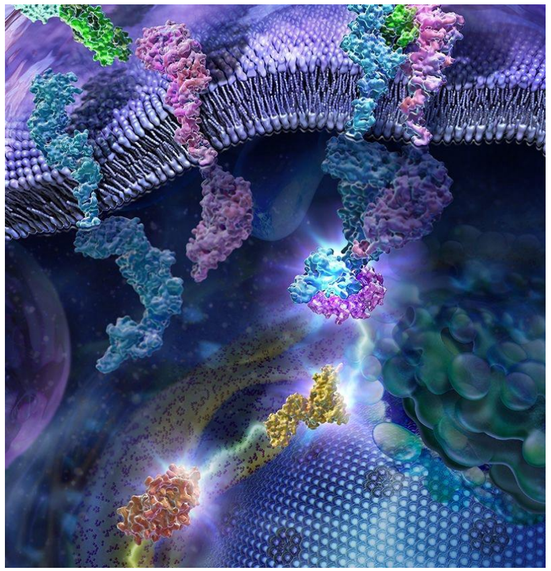
NOTE: Signaling components are: RECEPTION, TRANSDUCTION AND RESPONSE

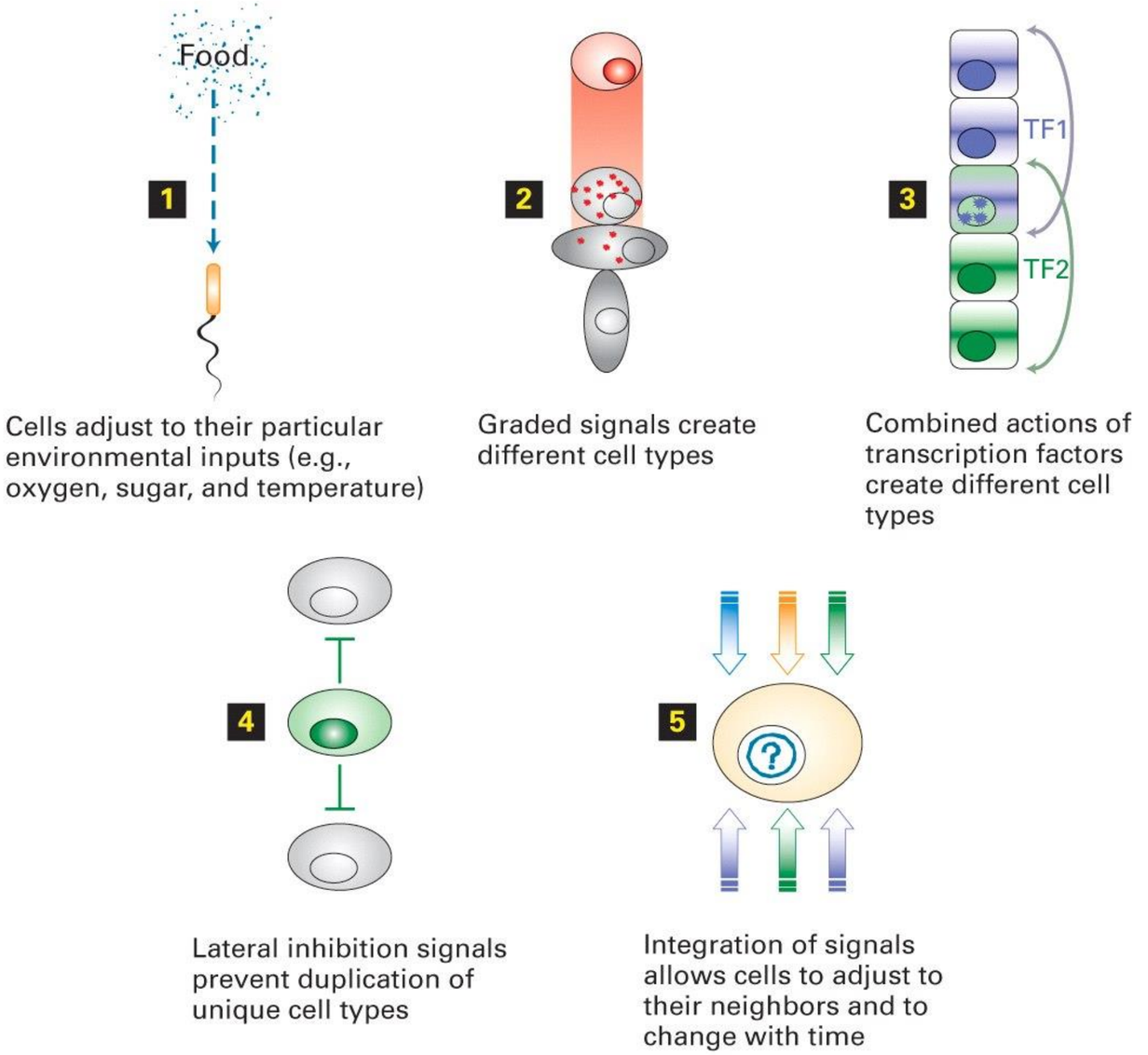
Signaling Overview

- There should be a reception which is the fitting between the ligand & the receptor

- The 2nd step is transduction, translating the information from the signaling molecule

- What should happen and what should the cell do is Cell response: activation, deactivation for some proteins or maybe producing some new proteins; cells can change their shape or movement and maybe they could die !

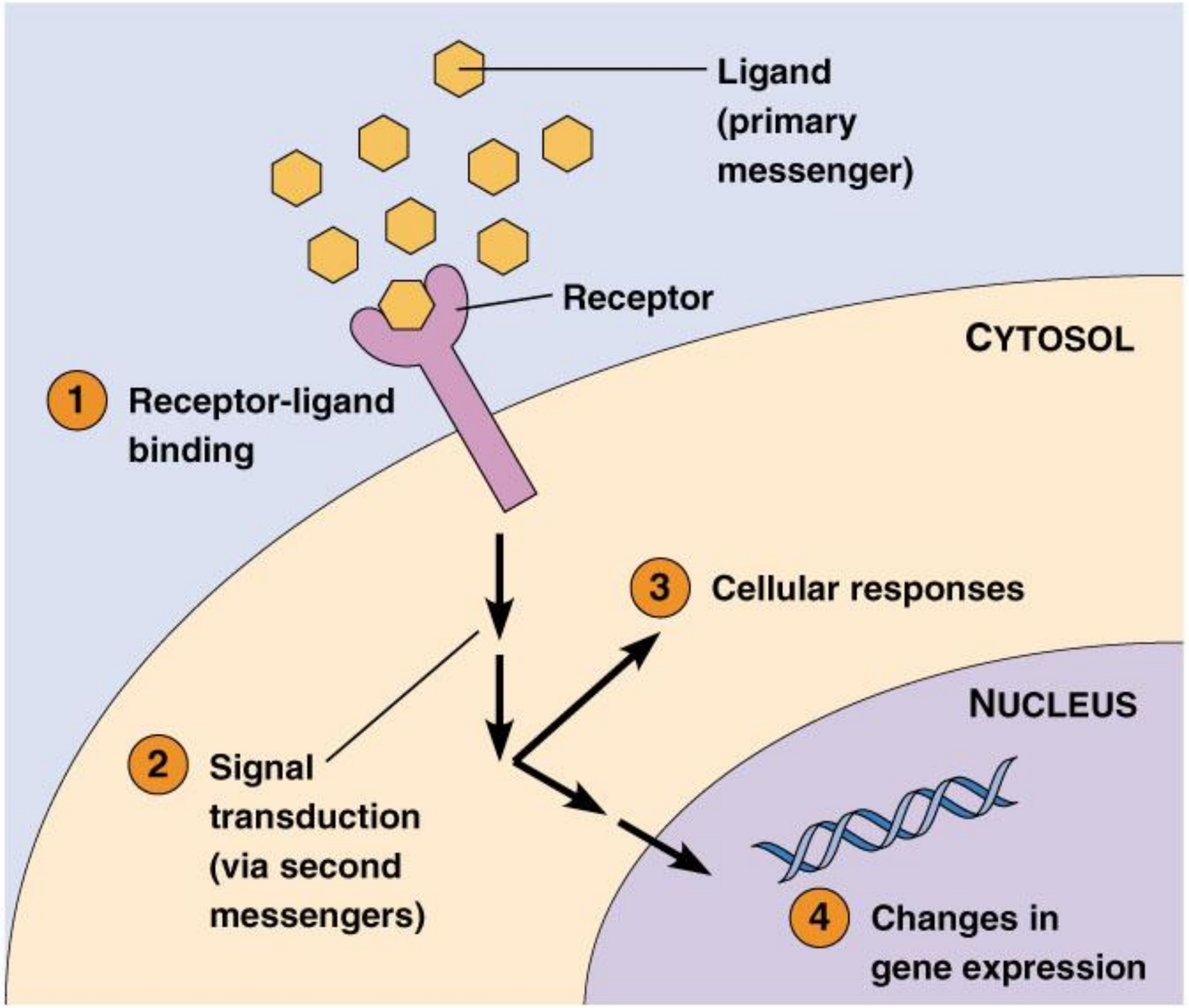




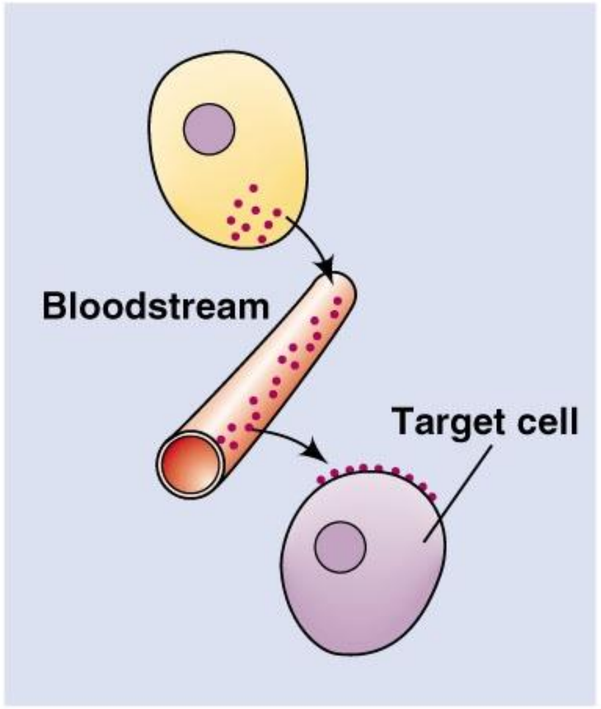
Signaling is responsible for how cells can respond to their environment and how they can differentiate or change over time

Signals get translated into cellular responses or changes in gene expression

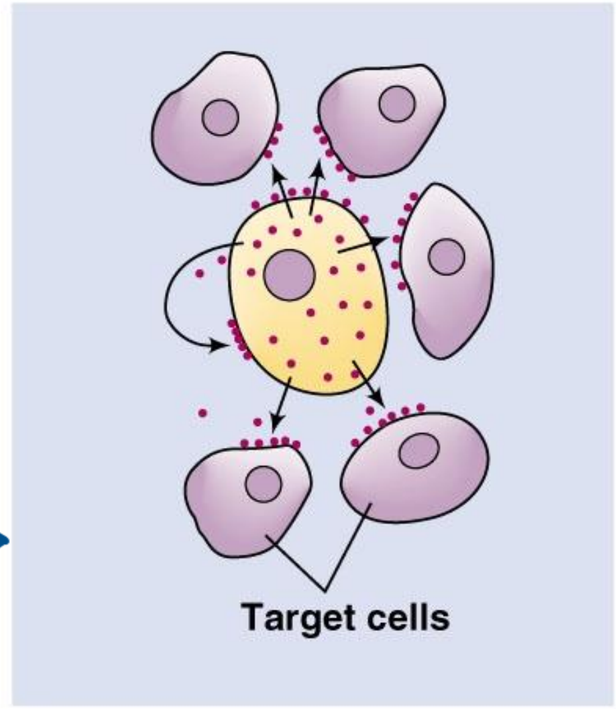
- Receptor is located on plasma membrane
- Receptor has two parts :
1. the extracellular part: which is responsible for *binding* to the ligand.
2. Where the intracellular one is responsible for *sending* these massages (that came from the ligand) into the cell.
- Massages could be translated into either activating an already present protein, producing a 2nd messenger or could act directly on GENE EXPRESSION.



Signals can act locally or at a distance



Hormones



Local mediators

We have cells all over our body and they all communicate with each other (brain sends signals to our toes for example, to our organs & to our glands such as the endocrine glands)

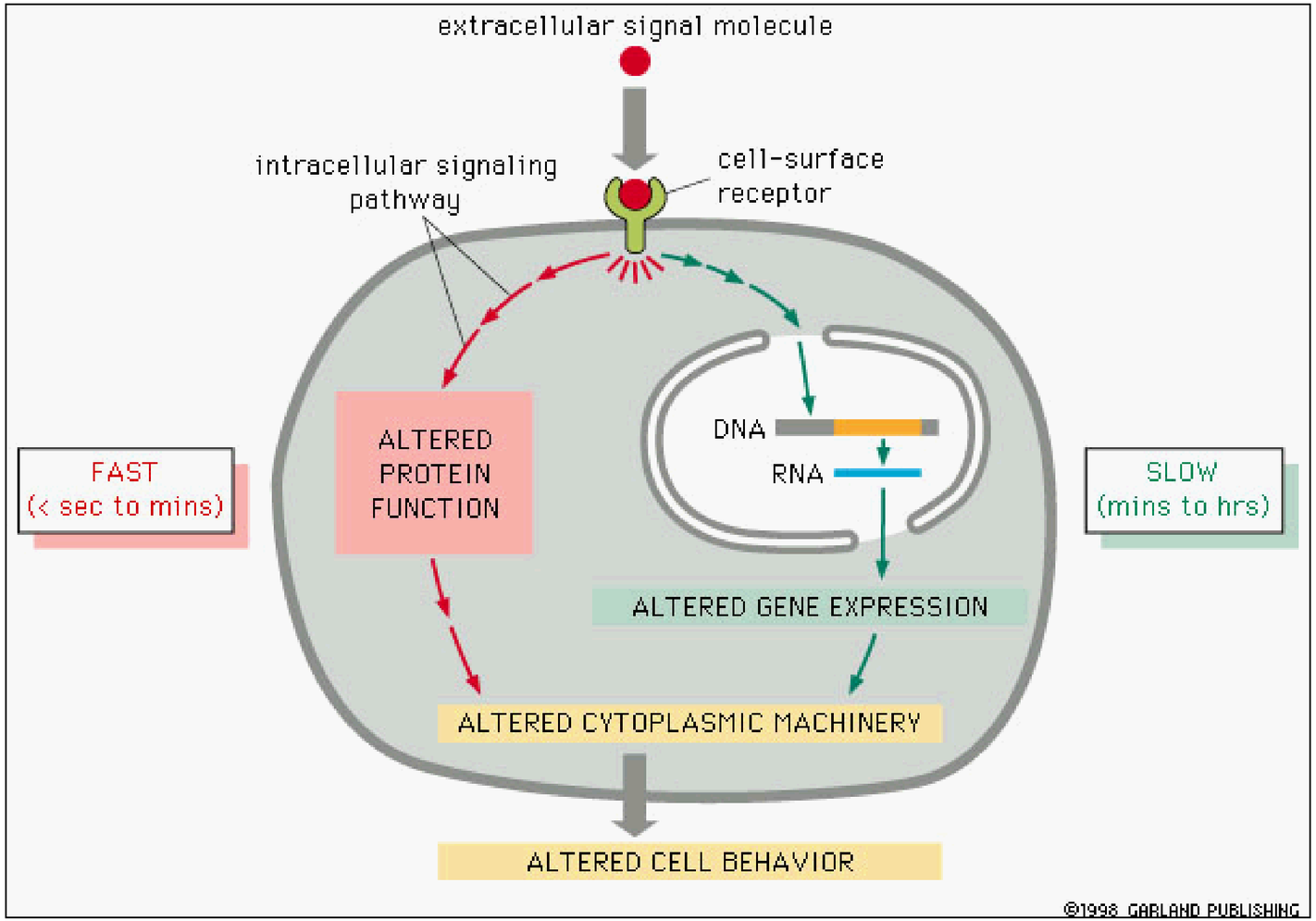
- pituitary gland sends Hormones to all over our body so these signals (Hormones here) are secreted into the blood stream (remember when we said that endocrine –> secrete to the blood stream in one of Dr. Khatatbeh's lectures).

Nearby secretion
At short distances
Locally where the target cells are just nearby the affecting cell
Paracrine signaling: Histamine (Immune system)
Source: Mast cells
Target: Nearby capillaries and immune cells.

Responses can be fast or slow

Depending on the pathways these signals are going through

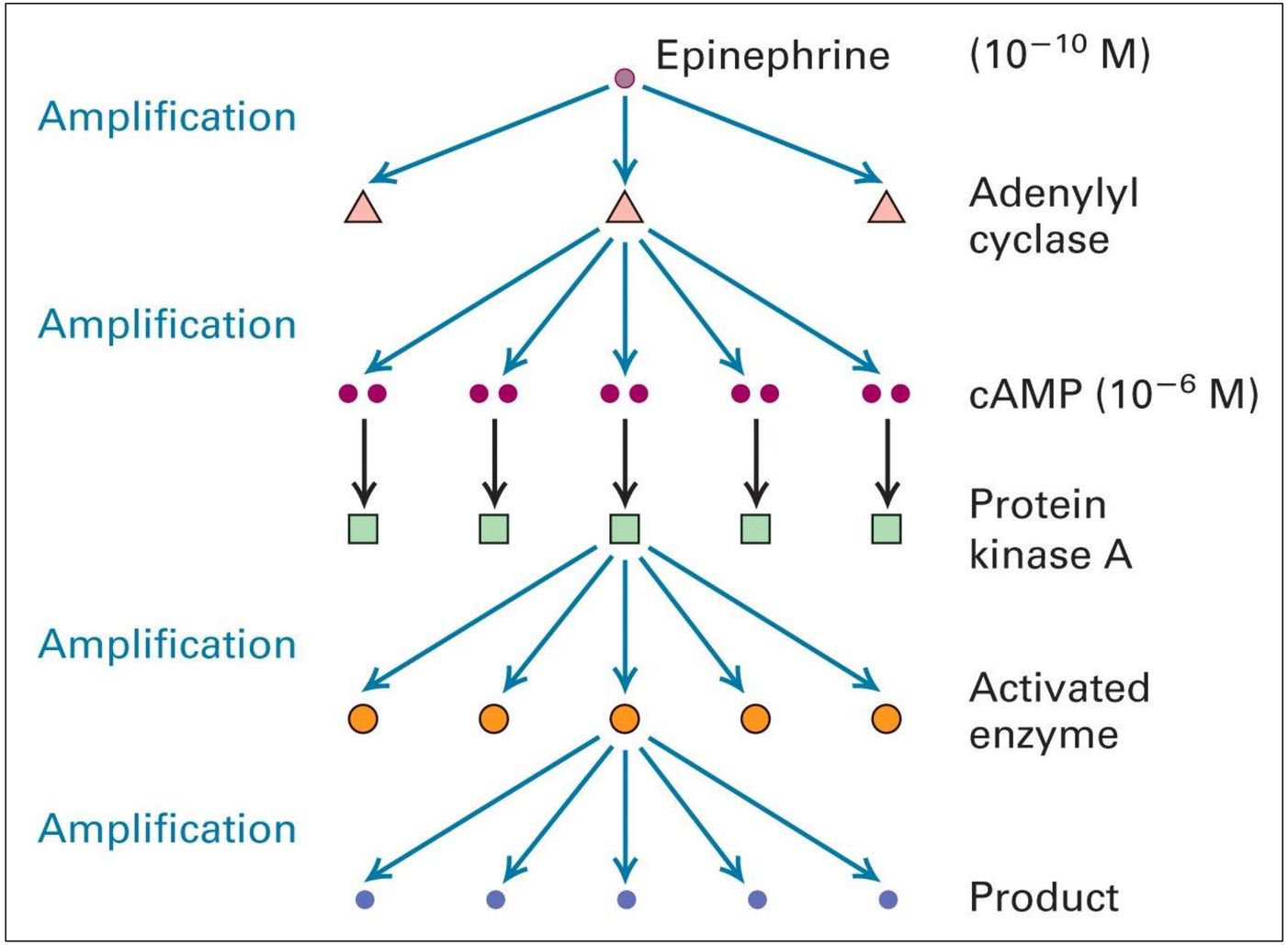
- If the signals go through GENE TRANSCRIPTION we expect it to be slow (synthesizing a new protein is not that easy/fast process as we know)
- But if they are affecting an already existing protein by Phosphorylating it could be a fast process, either activating or deactivating على حدّ سواء



Signals are amplified

signals can be amplified –this is a key feature of many biological signaling pathways and helps a small initial signal produce a **large** cellular response.

Signal amplification means that a few signaling molecules can generate a strong and **widespread** cellular response, allowing the body to react efficiently to even tiny stimuli.



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

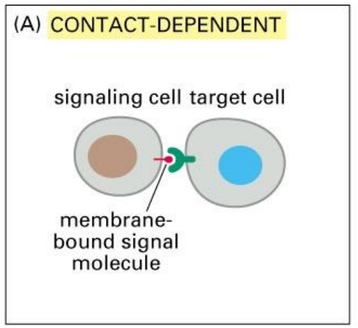
3. Growth factors (GF), i.e. NGF, EGF, PDGF

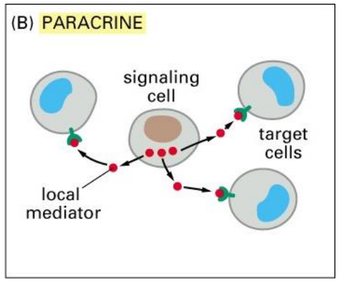
4. Lipophilic signaling molecules, i.e. prostaglandins

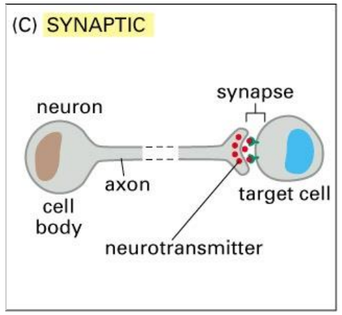
B. Ligands that bind to intracellular receptors:

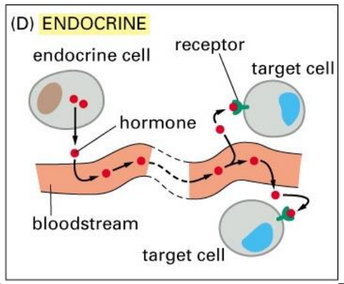
lipid soluble hormones that diffuse across the plasma membrane and interact with receptors in the cytosol or nucleus. i.e. steroids, thyroxine, retinoic acid, nitric oxide.

Types of Signaling





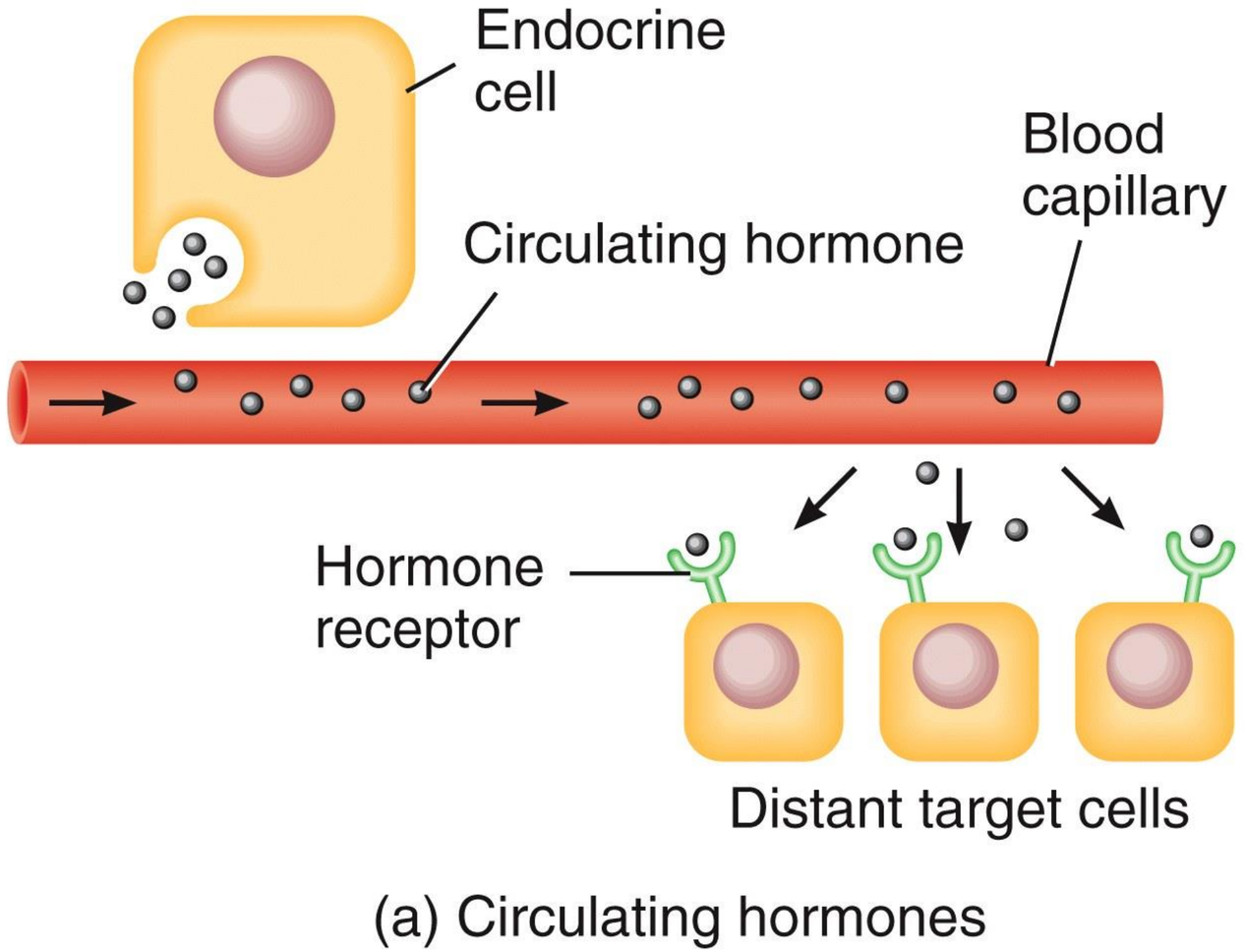




Types of Signaling

- **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

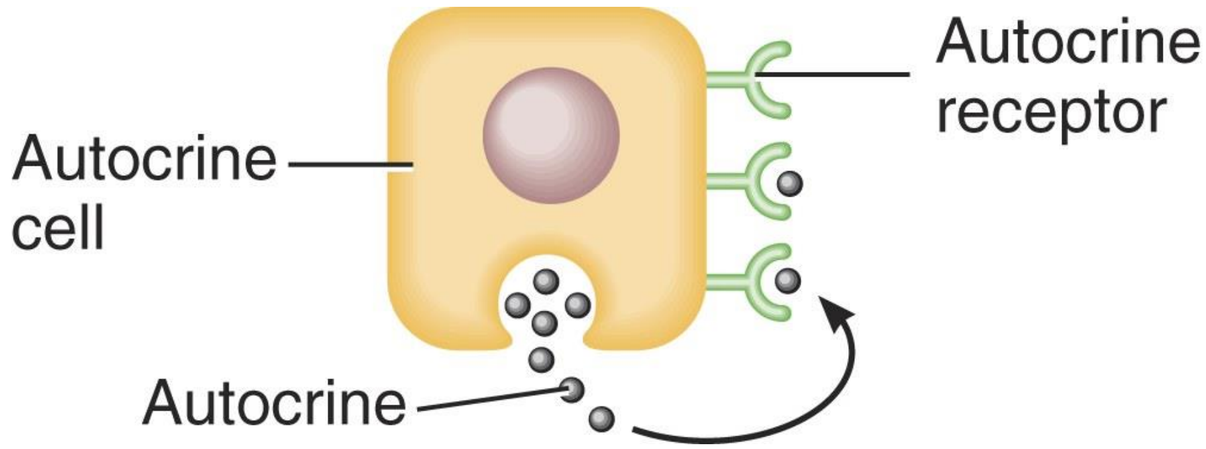
- **Autocrine**

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

- **E.g.** ınterleukin- 2 (IL-2),

  which is released by helper T

  cells.

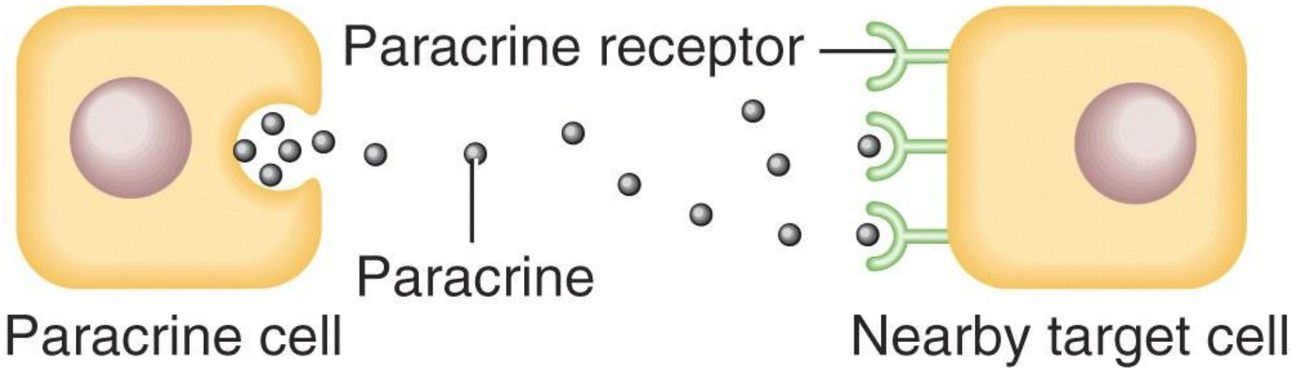


Types of Signaling

- **Paracrine**

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

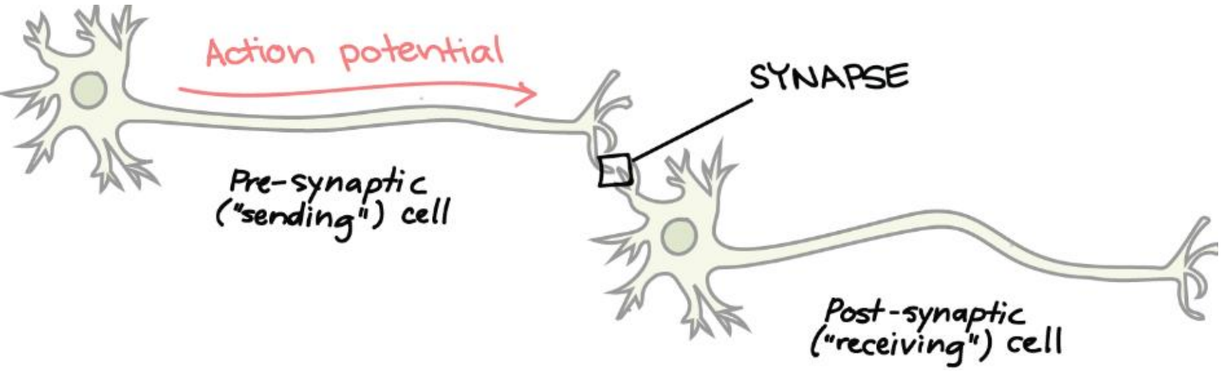
- **E.g. nitric oxide (NO).**

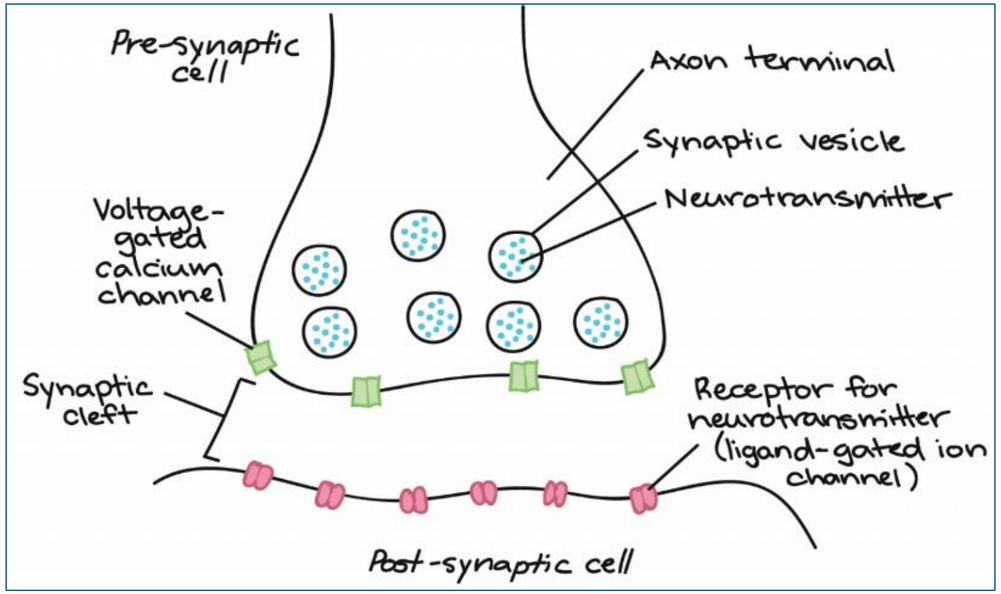


Quick Comparison Table:

Feature	Endocrine	Paracrine	Autocrine
Distance	Long (bloodstream)	Short (local tissue)	Very short (same cell)
Target cells	Distant organs/cells	Nearby cells	Itself
Example	Insulin, cortisol	Histamine, NO	IL-2, growth factors

Chemical Transmission at The Synapse

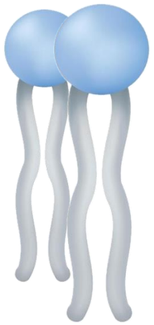




Chemical Classes of 

- 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).

T3 & T4 are secreted by Tyrosine (an amino acid) that bind with iodine

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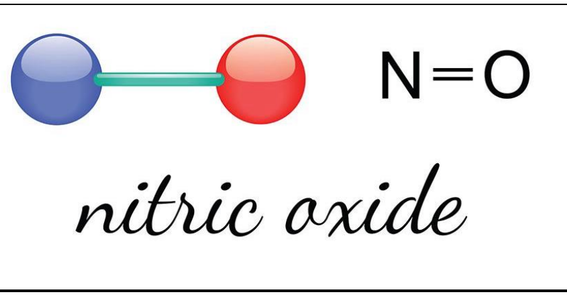
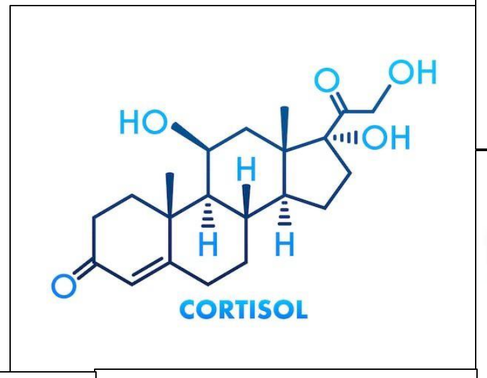
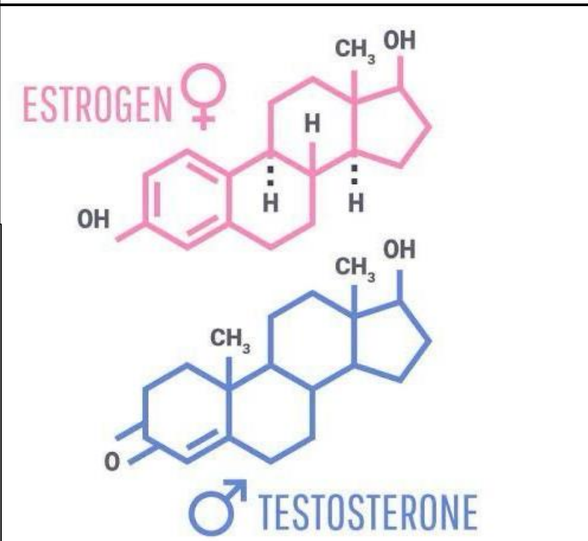
amino acids which are hydrophilic

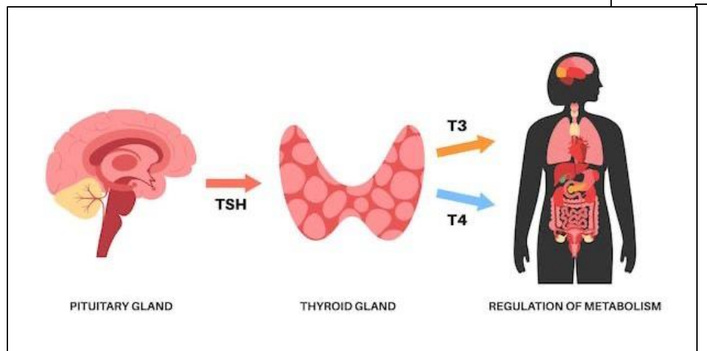
ليش بنعتبرهم lipophilic ؟

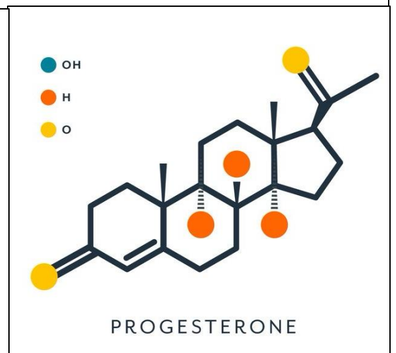
Cuz Thyroid hormone structure has benzene ring which is hydrophobic (lipophilic)



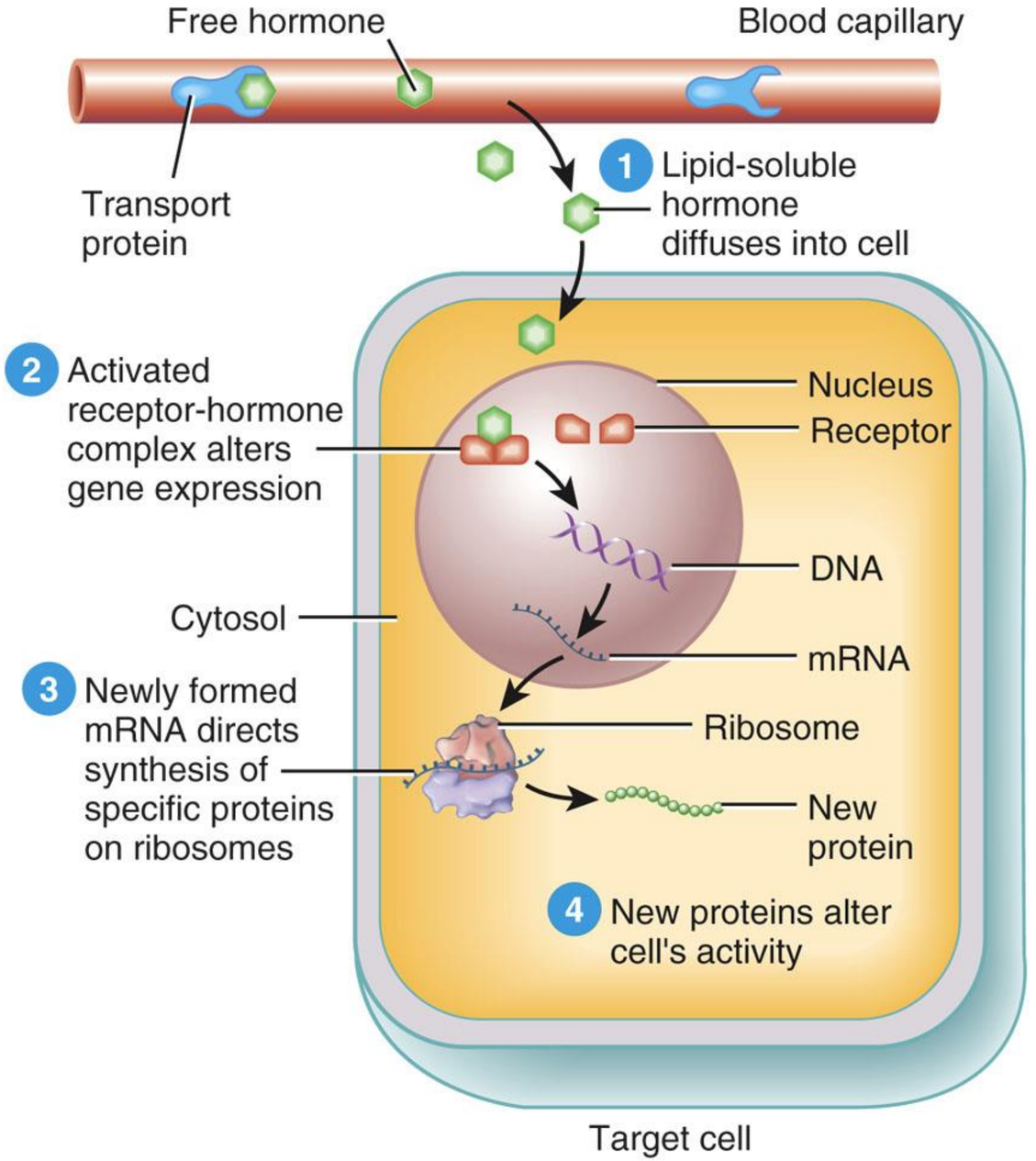








- **Lipid soluble hormones** require a carrier protein for transport in the watery environment of the blood
- Once they arrive at their destination, however, they are able to freely pass through the plasma membrane to bind to receptors located in the cytoplasm or the nucleus of the target cell



Water soluble hormones (Hydrophilic)

✓ Peptide hormones and protein hormones and glycoprotein 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

Polypeptide , protein and glycoprotein hormones .

- Most of the hormones in the body are polypeptides and proteins.
- These hormones range in size from small peptides with as few as three amino acids (e.g., thyrotropin-releasing hormone) to proteins with almost 200 amino acids (e.g., growth hormone and prolactin).
- In general, polypeptides with 100 or more amino acids are called proteins, and those with fewer than 100 amino acids are referred to as peptides

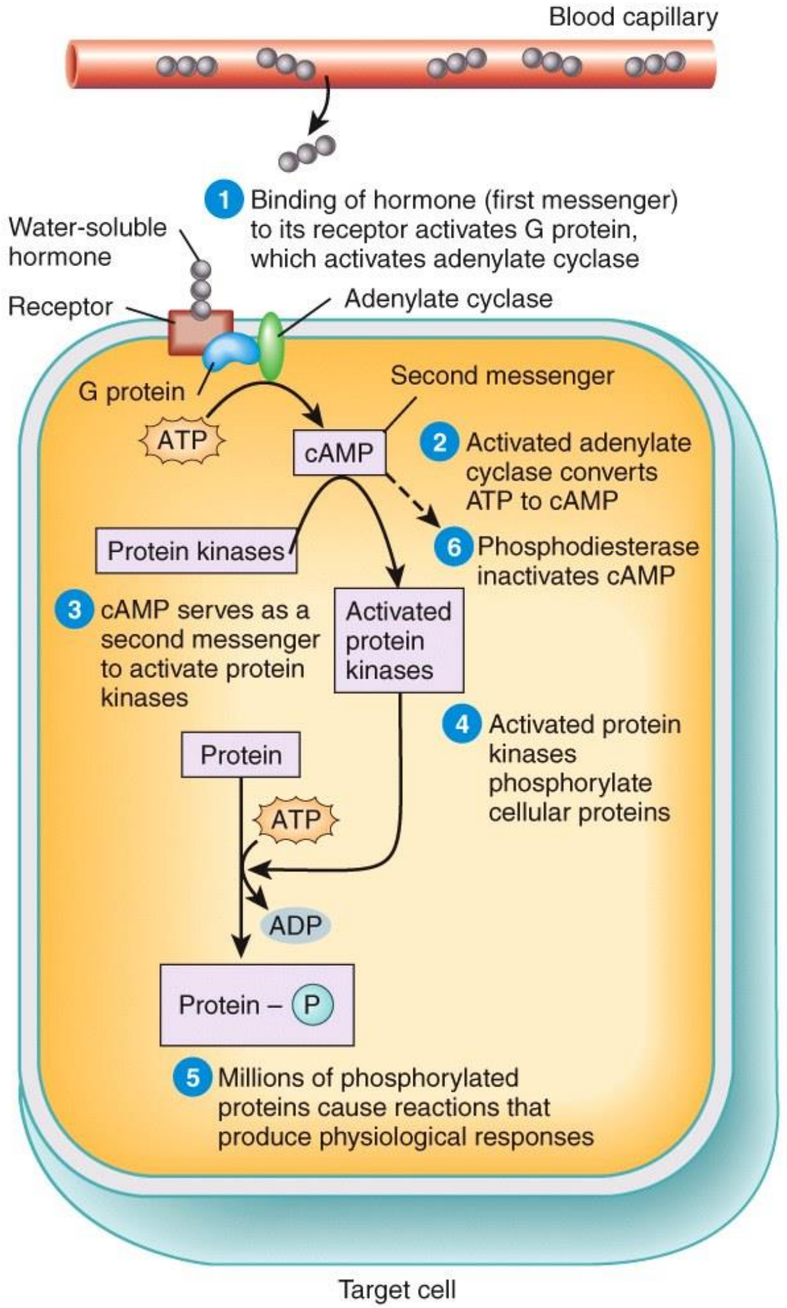
- the peptide hormones are water soluble, allowing them to enter the circulatory system easily, where they are carried to their target tissues.

- Peptide and protein hormones cant diffuse through the plasma membrane (phospholipid bi- layer)

- They bind to receptors on the plasma membrane (extracellular membrane receptors)

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.



G Protein-Linked Hormone Receptors.

- Many hormones activate receptors that indirectly regulate the activity of target proteins (e.g., enzymes or ion channels) by coupling with groups of cell membrane proteins called (G proteins)
- Some parts of the receptor that protrude into the cell cytoplasm (especially the cytoplasmic tail of the receptor) are coupled to G proteins that include three (i.e., trimeric) parts-the a, B, and y subunits.
- When the ligand (hormone) binds to the extracellular part of the receptor, a conformational change occurs in the receptor that activates the G proteins and induces intracellular signals

- Activation of G protein = release of GDP from the alpha subunit and binding of GTP

- The α subunit (with GTP) separates from the $\beta\gamma$ subunits. Both can interact with other proteins inside the cell.

G Protein-Linked Hormone Receptors.

- The α - GTP complex activates an enzyme like adenylyl cyclase, which converts ATP to cyclic AMP (cAMP)—a second messenger.

- cAMP activates protein kinase , which phosphorylates proteins (phosphate groups are full of energy), triggering a cellular response.

- The active G protein can either (1) open or close cell membrane ion channels, (2) change the activity of an enzyme in the cytoplasm of the cell, or (3) activate gene transcription.
- The trimeric G proteins are named for their ability to bind guanosine nucleotides. In their inactive state, the a, B, and y subunits of G proteins form a complex that binds guanosine diphosphate (GDP) on the a subunit.

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	Gland/Tissue	Hormones
Hypothalamus	■ TRH, GnRH, CRH GHRH, Somatostatin,	Placenta	■ HCG, HCS or HPL
Anterior pituitary	■ ACTH, TSH, FSH, LH, PRL, GH	Kidney	■ Renin (enzyme) ■ Ang II (peptide)
Posterior pituitary	■ Oxytocin, ADH	Heart	■ ANP
Thyroid	■ Calcitonin	G.I. tract	■ Gastrin, CCK, Secretin, GIP, Somatostatin
Pancreas	■ Insulin,Glucagon, Somatostatin		
Liver	■ Somatomedin C (IGF-1)	Adipocyte	■ Leptin
Parathyroid	■ PTH		

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)

- Amine Hormones are derived from tyrosine

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)

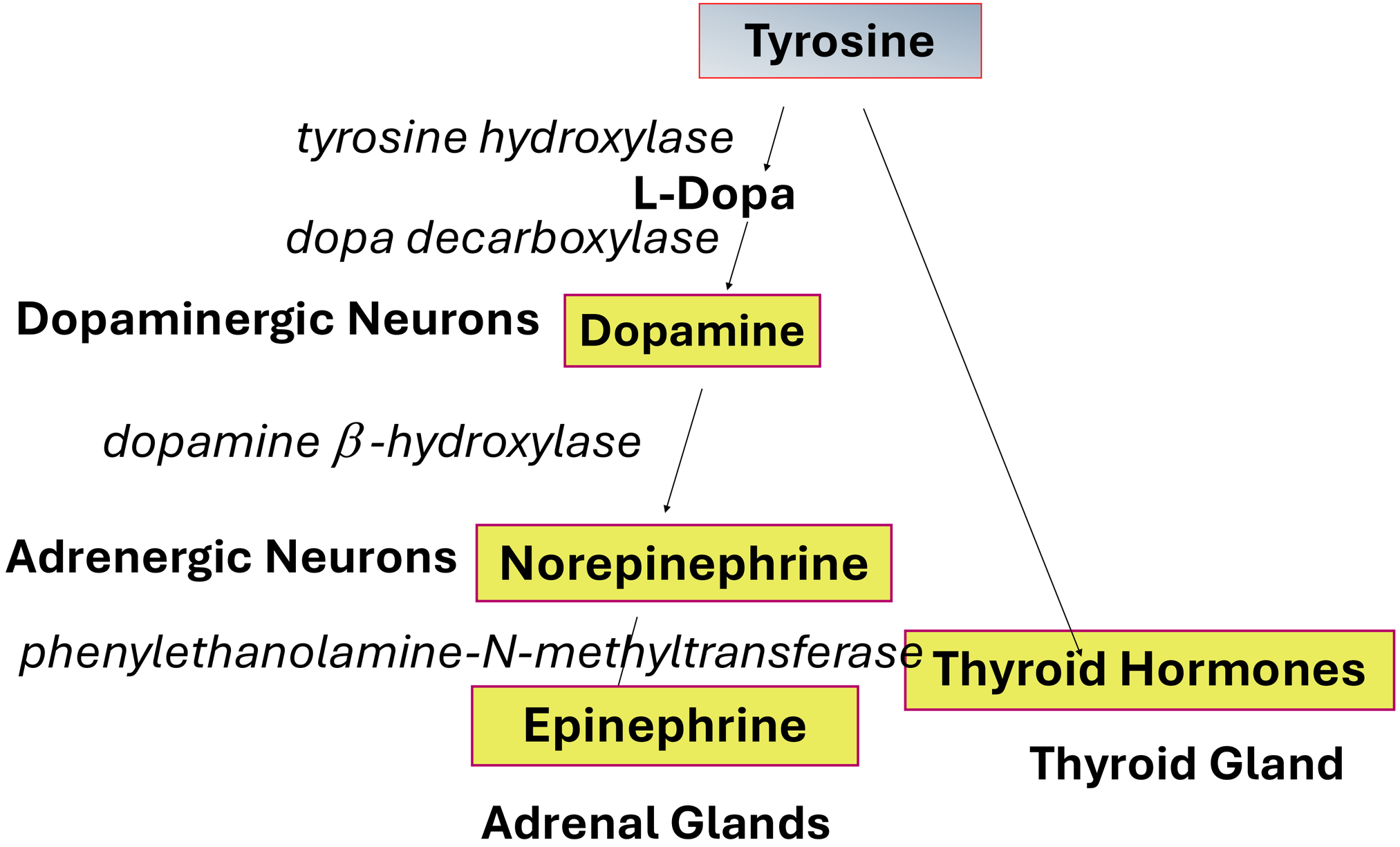
Chemical classes of hormones

- 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



Synthesis of Amine Hormones

1. In the Thyroid Gland:

- Tyrosine combines with iodine
  → Produces thyroid hormones:
  T3 (triiodothyronine) and T4 (thyroxine)
  these regulate metabolism and energy

Pathway Summary:

- Tyrosine → L-DOPA → Dopamine → Norepinephrine → Epinephrin
- Tyrosine → Thyroglobulin + Iodine → T3 and T4

2. In Dopaminergic Neurons:

Tyrosine → converted by tyrosine hydroxylase to L-DOPA
L-DOPA → converted by DOPA decarboxylase to Dopamine
Dopamine acts as a neurotransmitter involved in mood, reward, and movement.

3. In Adrenergic Neurons:

Dopamine → converted to Norepinephrine (Noradrenaline)
Norepinephrine regulates alertness and the “fight or flight” response.

4. In the Adrenal Medulla (part of adrenal gland):

Norepinephrine → converted to Epinephrine (Adrenaline)
Epinephrine acts as a hormone that prepares the body for emergency responses.

Prohormones and Prehormones

Not all hormones produced in the body are immediately active. Some are initially produced as prohormones or preprohormones, which require further processing to become biologically active.

- Prohormone
  - Precursor is a longer chained polypeptide that is cut and spliced together to make the hormone.
    - Proinsulin – gives insulin

      insulin is produced initially as proinsulin, which consists of insulin itself plus a C-terminal segment. It needs to undergo cleavage (slicing) to release the active insulin.
- Preprohormone:
  - Prohormone derived from larger precursor molecule.
    - Preproinsulin.

      This is an even earlier form than a prohormone. For example, insulin is first produced as a preproinsulin. The “pre” segment is usually a signal peptide that guides the protein to its proper location and is later removed during activation.
- Prehormone:
  - Molecules secreted by endocrine glands that are inactive until changed into hormones by target cells.
    - T_4 converted to T_3 (tri-iodothyronin).

Hormones and Their Activation

- Example: Thyroid Hormones (T3 and T4)
- The thyroid gland releases two main hormones: T3 (triiodothyronine) and T4 (thyroxine).
- T4 has four iodine atoms and is the inactive or storage form of the hormone.
- T3, with three iodine atoms, is the active form.
- Although the thyroid secretes some T3, most of it comes from the conversion of T4 to T3 in peripheral tissues by removing one iodine atom.

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.

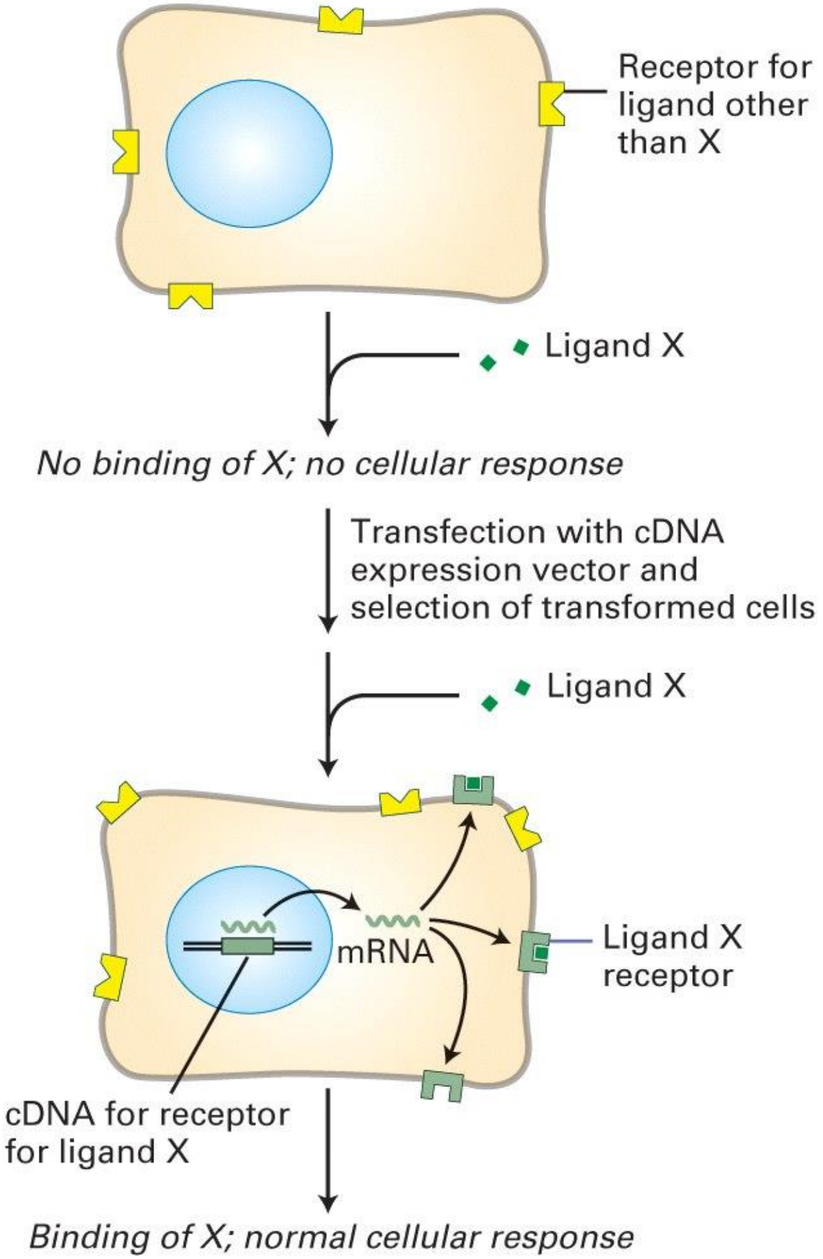
Glycoprotein or Lipoprotein

Receptors determine response

No receptor - no response

- It’s the receptor, not the ligand, that determines the specific cellular response.
- A ligand (such as a hormone or neurotransmitter) is a molecule that binds to a receptor on or inside a cell.
- The same ligand can bind to different types of receptors on different types of cells, leading to different responses.

So, it's not the ligand that causes different effects, but the receptor type and the cell context.



Hormone-Receptor Interaction

- Hormones exert their effects by binding to specific receptors on or inside target cells.

- The receptor is a protein that must match the shape and chemical characteristics of the hormone (ligand) for binding to occur.

- If a hormone arrives at a cell without a suitable receptor, no response will occur — "No receptor, no response."

- Example:
  If a ligand (e.g., ligand X) cannot bind to the receptor on a cell, no cellular response occurs. However, if the cell is genetically modified (e.g., using a virus to introduce a DNA sequence that encodes the receptor for ligand X), the receptor gets expressed. Then, ligand X can bind and trigger a cellular 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.

NOTE: For a receptor, “specificity” describes how much the receptor favors a particular ligand relative to the other ligands that may also be present. In real biological systems the specificity of either ligands or receptors is rarely 100%- this is one of the reasons why drugs tend to have side effects. For example, it is well known that most proteins that bind a given nucleotide (like ATP) are not completely specific for ATP, but can bind a variety of ATP analogs like thio-ATP, AMPPCP, or even GTP.

The association constant is a measure of the degree of reversible association between two molecular species in equilibrium. The dissociation constant is the rate constant of equilibrium dissociation. In pharmacology, the main factors affecting the dissociation constant are temperature and the presence of catalyst

Location of receptors

(depends on the chemical nature of the ligand)

- **Membrane receptors**

Membrane Glycoprotein

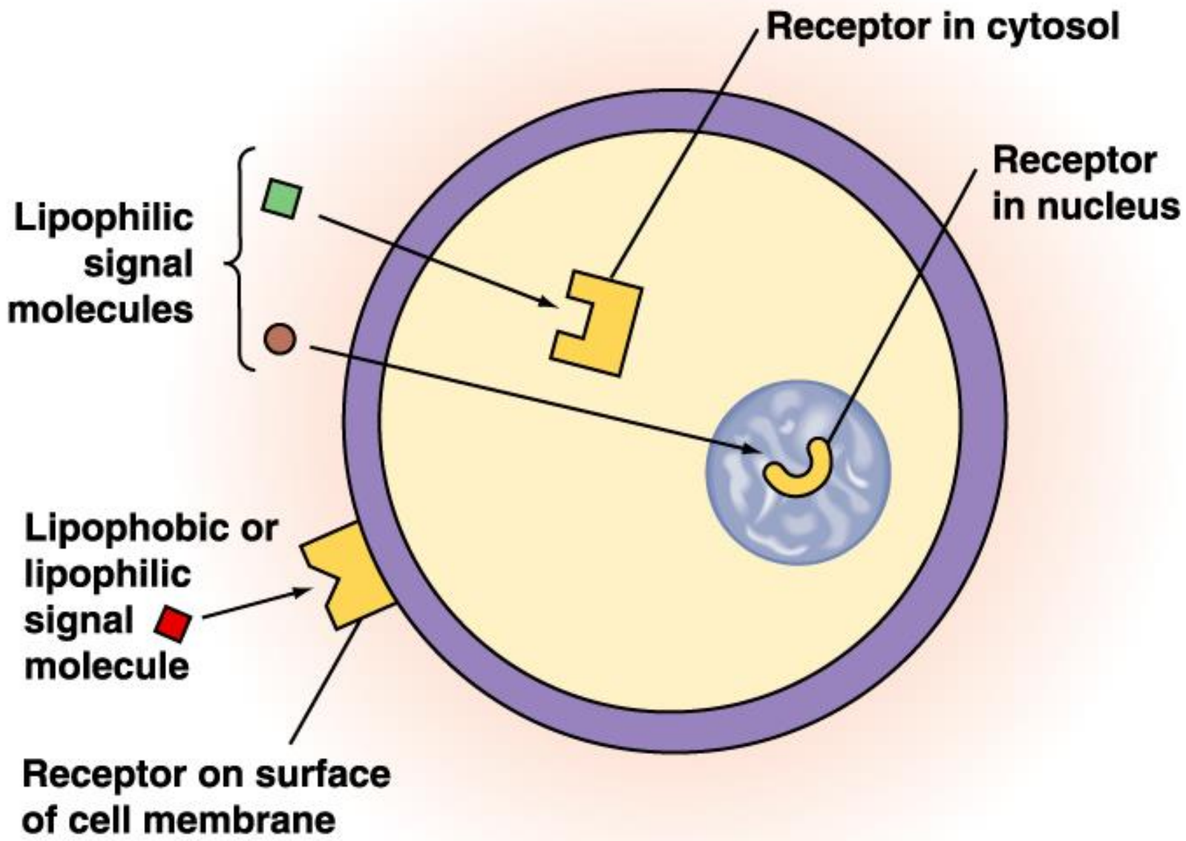
for water-soluble hormones (e.g., insulin).

- **Intracellular receptors**

Cytosol or nuclei

DNA binding protein

for lipid-soluble hormones (e.g., steroid hormones or thyroid hormones).



Mechanisms of Hormone Action

- Response depends on both hormone and target cell
- Lipid-soluble hormones bind to receptors inside target cells

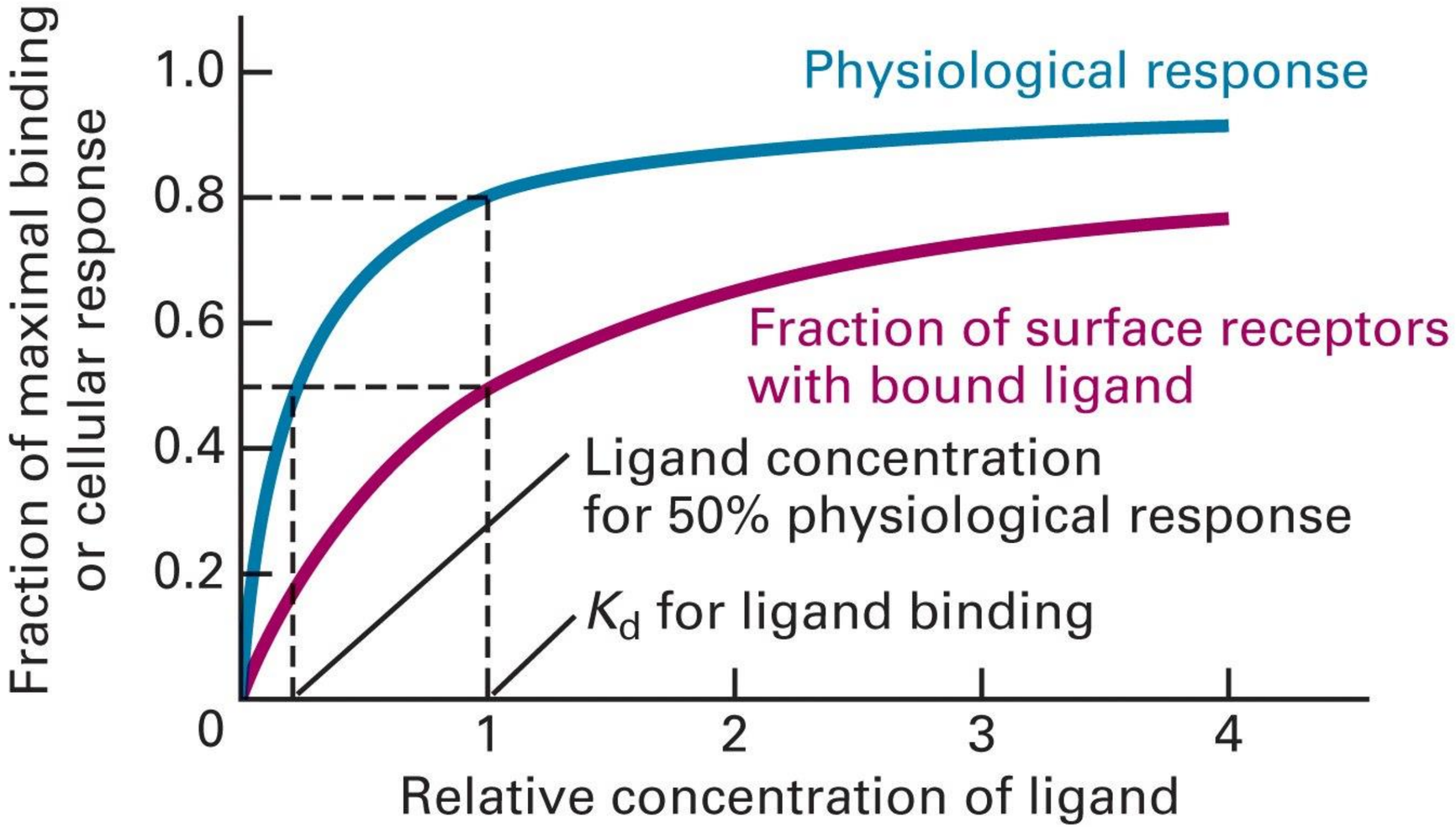
(e.g., steroids): cross the membrane, bind intracellular receptors, and affect gene expression.

- 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



- Factors Influencing Cellular Response to a Hormone

- Hormone concentration.
- Number of receptors on the target cell.
- Presence of other hormones:

1. Synergistic effect: Enhances the hormone's action.
2. Antagonistic effect: Inhibits or reduces the hormone's effect

- Hormone Concentration and Response Curve

The response increases with more hormone and more binding.

However, not all receptors need to be bound to get a maximum response, due to signal amplification (triggers a cascade of intracellular reactions , So, even if only a small fraction of receptors on a cell are activated, the downstream signaling cascade can produce a large physiological response.)

-Beyond a certain point, increasing hormone concentration won't increase the 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.
      - Loss of sensitivity to the hormone
        - Insulin in adipose cells.

  - Pulsatile secretion may prevent downregulation.

  - This explains conditions like insulin resistance in adipose tissue with chronic high insulin levels.

Signaling Overview

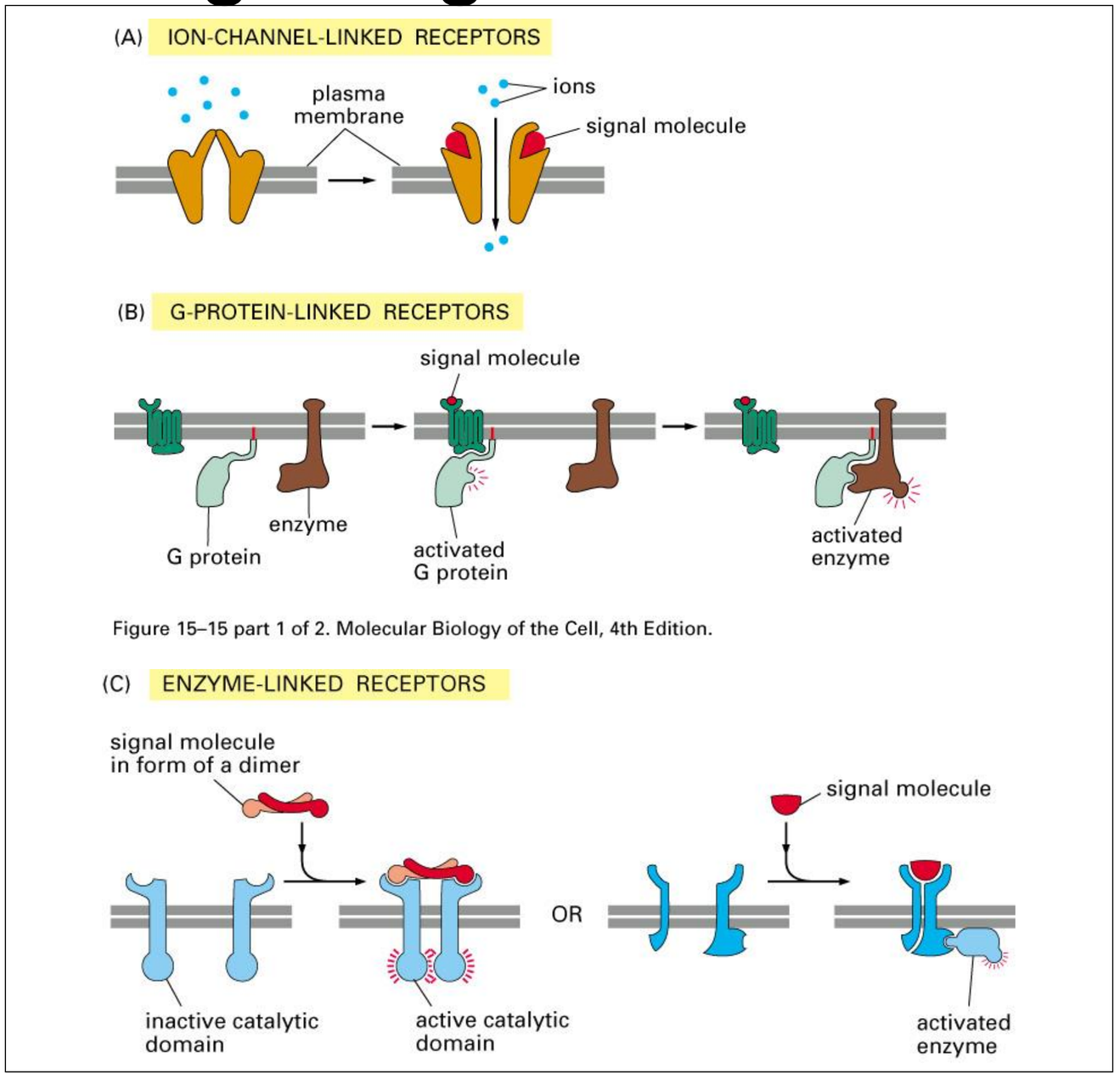


Figure 15–15 part 1 of 2. Molecular Biology of the Cell, 4th Edition.

Desensitization in Therapy

- Allergy desensitization: Exposing a person to small, repeated doses of an allergen reduces receptor sensitivity over time.

- Therapeutic sensitivity restoration: To reverse desensitization, the hormone should be administered intermittently (pulsatile fashion), allowing the receptors to recover and resensitize.

Types of Receptors and Signaling Mechanisms

1.Ion channel-linked receptors

2. G-protein coupled receptors (GPCRs)

3. Enzyme-linked receptors

Additional Resources:

رسالة من الفريق العلمي:

- بأندلسٍ فتحناها وأندلسٍ سنفتحُها
لنشرِ الحقّ للدّنيا ونَفض غُبارها عنها
سنحكي عن ملاحمِنا بأرضٍ عزُّها معها
لقُدسِ المسجدِ الأقصى إذا التاريخُ ما ذُكِرَ
فذي أرضي وذا وطني عَلَتهُ كرامةٌ وبهاء
سَلوا التّاريخ عن عُمر، صلاحَ الدين والفُتّاح
أمينَ الأُمّةِ الأولى أبي عبيدةَ الجرّاح

For any feedback, scan the code or click on it.

Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1	Slide 46 moved to slide 37		
V1 → V2	Slide 40 added Slide 3 : note added		