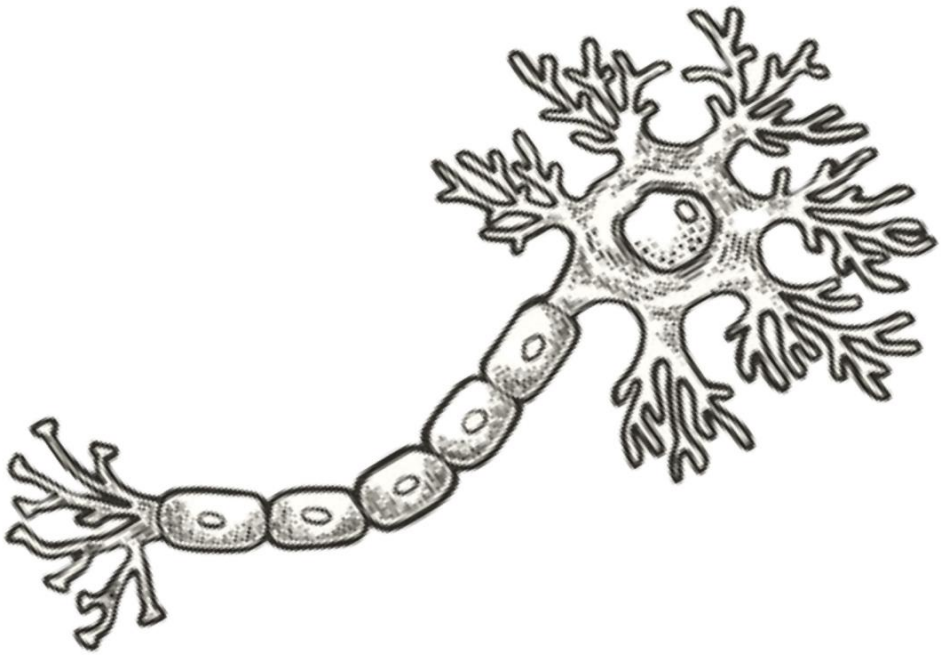
PHYSIOLOGY

SHEET NO.

16



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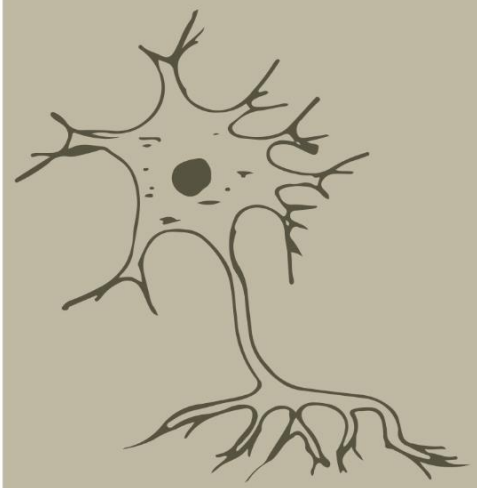


Signal transduction

1) Important definitions

-Signal transduction: process of converting extracellular signals into intracellular responses.

-Signaling: cell-cell communication via signals.

-Ligand: the signaling molecule.

-Receptors: specific proteins that bind to specific ligands, these proteins when binding transmit signals to intracellular target.

- Receptors can respond differently to the same ligand
- The actions (intracellular responses) depend on **ligands and receptors types**, sometimes the same ligand can bind to different types of receptors, but each one gives a different response according to the type of receptor the ligand binds to.

2) Compartments involved in signaling

ST: Signal transduction

A) Ligand

B) Receptors

C) Intracellular signaling proteins (mediators):

- Help in **ST** by transmit signals to the target proteins.

- They are inside the cell.

D) Target proteins:

- The proteins that are at the end of **ST** and the change occurs in them.

Examples on target proteins

- Metabolic enzymes ⟶ altered metabolism

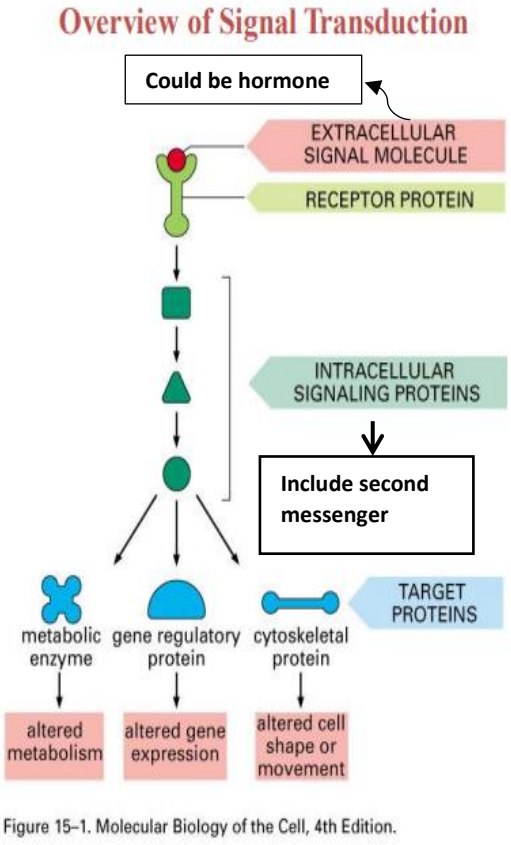


Figure 15–1. Molecular Biology of the Cell, 4th Edition.

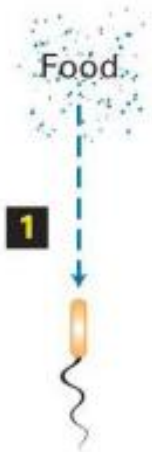
- Gene regulatory proteins ⟶ altered gene expression

- Cytoskeletal proteins ⟶ altered cell shape or movement

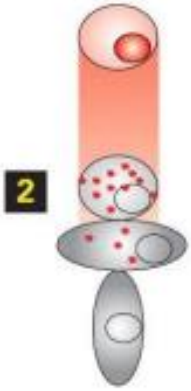
E) Intermediary proteins F) Enzymes G) Second messengers H) Inactivating proteins

E, F, G, H will be discussed later

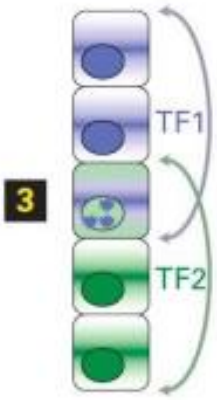
3) Functions of signaling



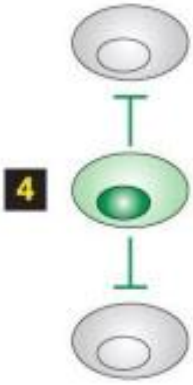
Cells adjust to their particular environmental inputs (e.g., oxygen, sugar, and temperature)



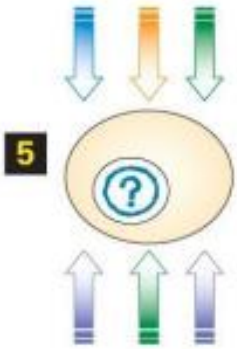
Graded signals create different cell types



Combined actions of transcription factors create different cell types



Lateral inhibition signals prevent duplication of unique cell types



Integration of signals allows cells to adjust to their neighbors and to change with time

Explanation of the five points in the picture above

1- Cells respond to environmental changes in order to maintain homeostasis such as: change in **oxygen, sugar, temperature** availability.

2- Sometimes the signal is not only a **switch on/off**, sometimes we have graded signals.

- Graded signals may induce cells to differentiate into different types of cells.

- Different **intensities (شدة)** of certain signal can have **different outcomes** or effects on cells.

3- Different combinations of signals can create different types of cells and that's also important for **cells differentiation**.

4- Signals are not always **excitatory,** sometimes the signal can be **inhibitory**

- Inhibitory signals can stop some mechanisms such as duplications, proliferation,…etc.

5- Different signals **integrate** and together help the cell to adjust to neighbors and change with time.

SO WE CONCLUDE THAT Signaling is responsible for how cells can respond to their environment and how they can differentiate or change over time.

4) Signals get translated into cellular responses or change in gene expression

The main mechanism for cell signaling:

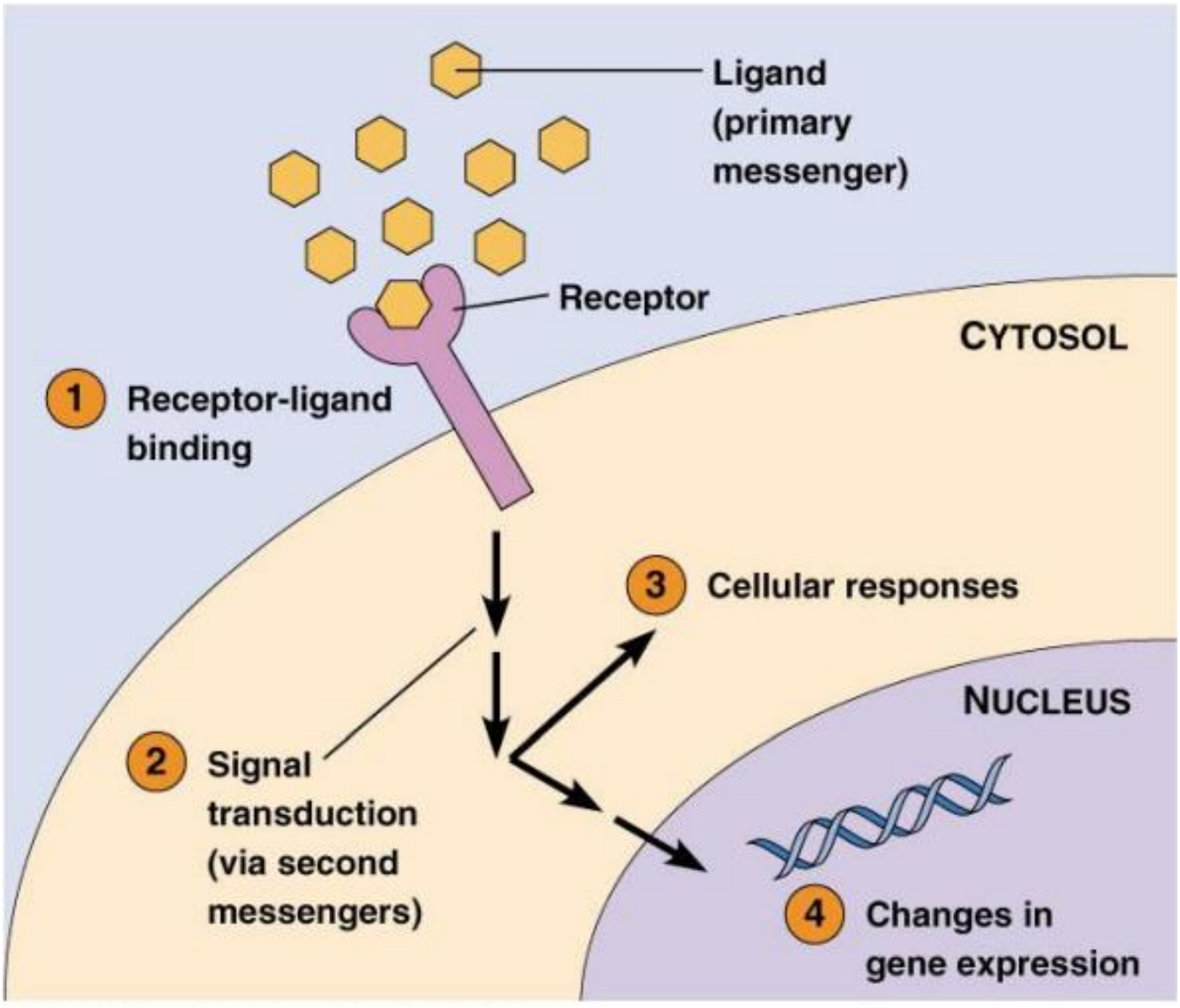
1- Ligand is secreted by secreting cell such as gland.

2- The ligand will find a receptor that is specific to this ligand.

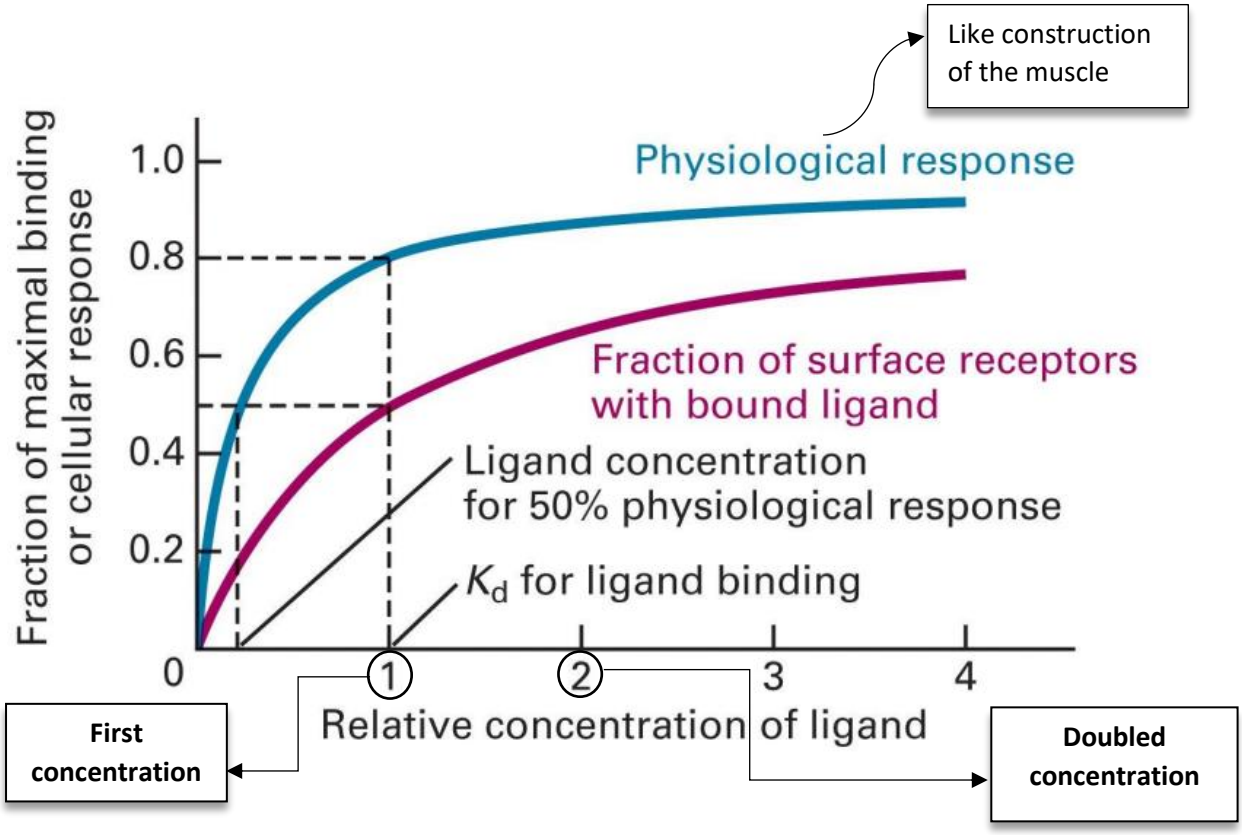
3- Receptor-ligand binding will induce changes **(structural, conformational)** in the receptor.

4- Other proteins inside the cell will be induced and changed (second messengers then target proteins) that will:

A. Transduce changes into cellular response.
B. **Or** go directly into the nucleus to induce changes in gene expression and production of receptors, enzymes or different protein.



5)



Do we need all receptors to be bound to their ligand in order to have physiological (cellular) response?

PR: Physiological Response

Just Understand :)

To answer this question let's take the **first concentration** in picture above which is the normal concentration of a ligand, you can see that even with 50% of receptors bound to their ligand we can have **nearly maximal PR** (in the pic above its almost 80% (0.8)).

When **concentration of the ligand is doubled** of course this will induce more binding, so we will get about 65% of receptors bound to their ligand, the **PR** is about 90%, so even at lower concentration of the ligand we could achieve very close to the maximal **PR** and even we doubled the amount of the ligand we didn't get that much increases in the maximal response, it **only** increased for maybe less than 10%.

SO WE DON'T NEED TO HAVE ALL THE RECEPTORS TO BE BOUND TO THEIR LIGAND IN ORDER TO INDUCE A GOOD PR.

بالمختصر ما بنحتاج انه تكون كل المستقبلات مرتبطة بأجسام محفزة (اللي بترتبط بالمستقبلات)، بس تركيز بسيط من الأجسام المحفزة كافي لإحداث استجابة.

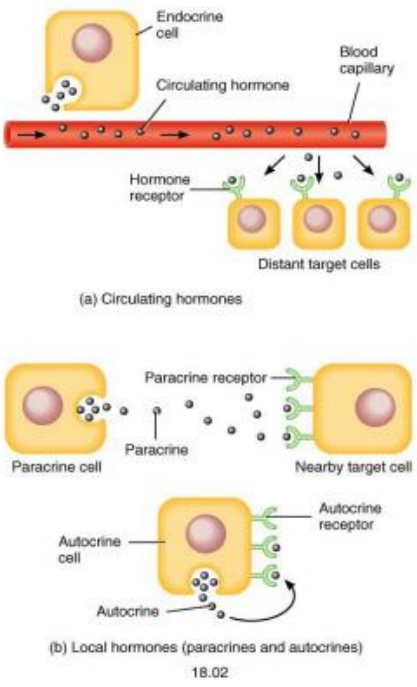
6) Signals can act locally (local mediators) or at a distance (circulating)

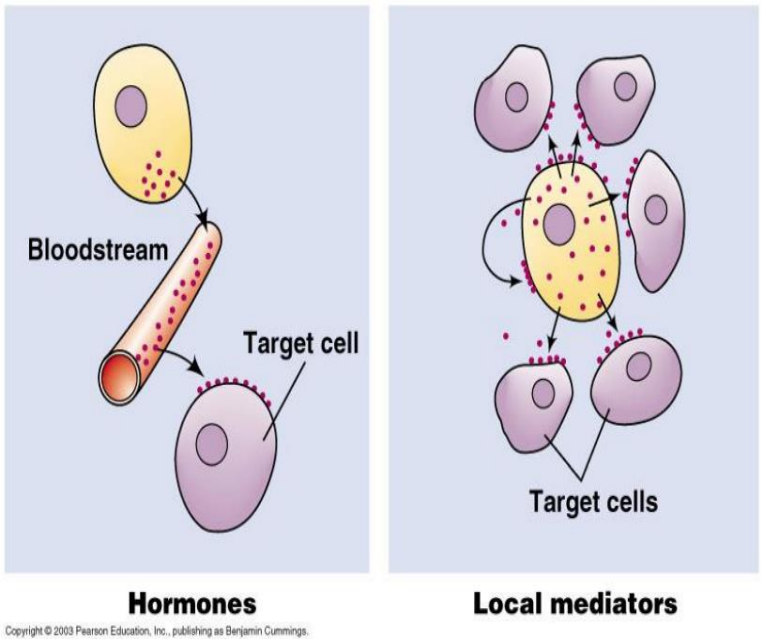
A) Signals that act locally (local mediators):

Signal is secreted by a cell and the target is **neighboring cell**, so signal acted through short distance from secreting cell and then bound to the receptor on the target cell that are very close to the secreting cell, **THEY ARE PARACRINE AND AUTOCRINE**.

B) Signals that act at a distant (circulating):

Some ligands are secreted from secreting cells (such as pituitary gland in the brain) and transported via blood stream (because there is no duct in this type) to a **distant target cell**, **THEY ARE ENDOCRINE SIGNALS**.

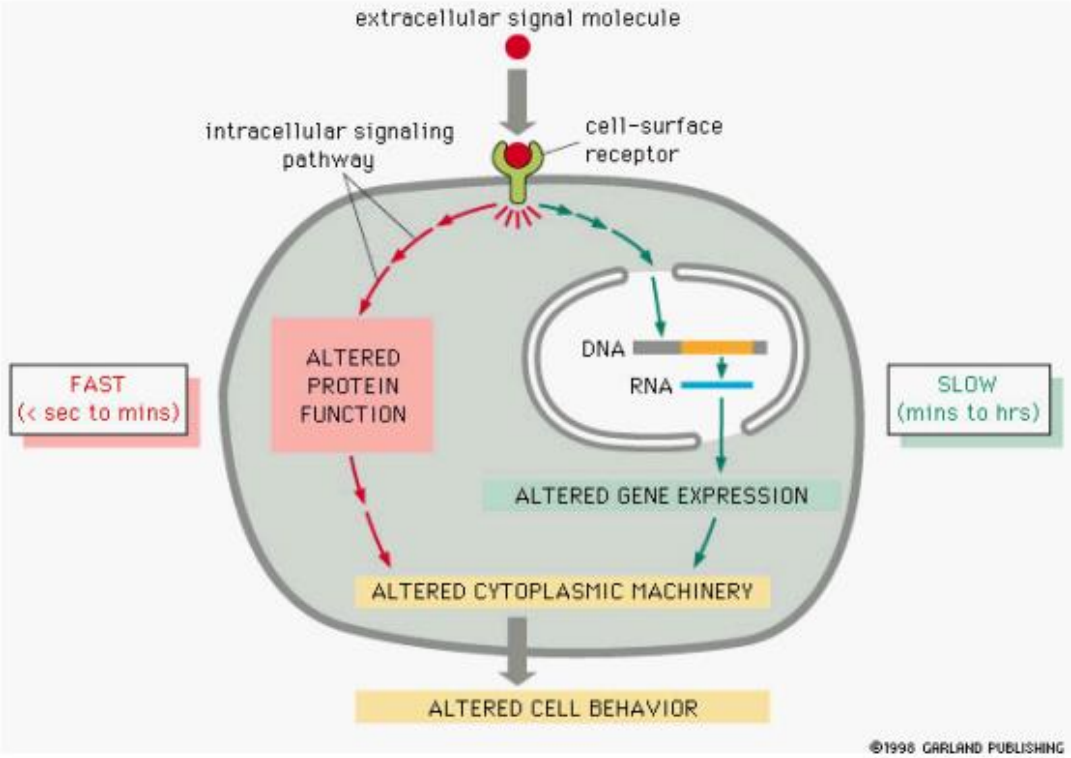




- The ligands that are secreted from a gland that hasn't a duct are called **endocrine** hormones (ligands).
- The ligands that are secreted from a gland that has a duct are called **exocrine** hormones (ligands).

This was discussed in Histology midterm :)

7) Responses can be fast or slow



Fast response	Slow response
It happens in **cytoplasm**	It happens in **nucleus**
Takes sec to few mins	Takes minutes to hours and maybe days
Fast when the response require **simple modification** (activating or deactivating) of **pre-existing protein** or change of cytoskeleton shape	Slow when the response require **altering gene expression** to generate new proteins

8) Signals are amplified

- Signal amplification allows for small initial signal to have a large downstream effect (one molecule in a single step can activate more molecules in the next step).

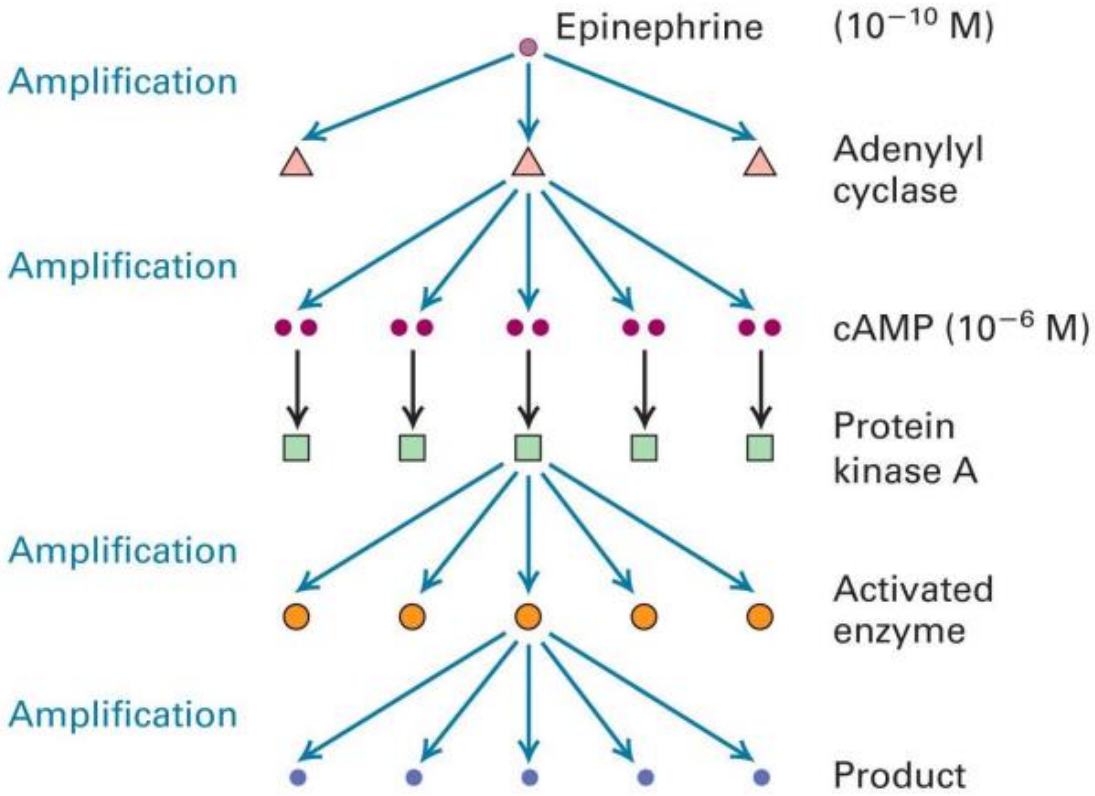
An example (**just to understand**):

Epinephrine ligand secreted from the adrenal medulla binds to their specific receptor causing conformational changes, this will induce (activate) many adenylyl cyclase, each adenylyl cyclase will generate many cAMPs, each cAMP binds to protein kinase A, and each protein kinase A will activate (phosphorylate) many enzymes, each one will give us many products.

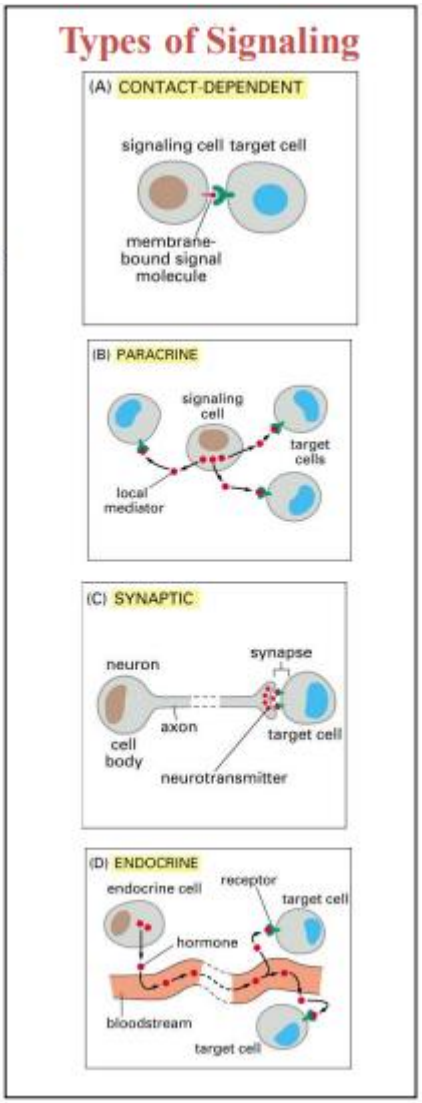
SO, AS YOU CAN SEE WE STARTED WITH ONE LIGAND AND ENDEDUP WITH SO MANY PRODUCTS.

This also answer the question above, do we need all the receptors to be bound to their ligand in order to have a good response?

No, because signals are amplified.



9) Types of signaling



1-Contact-dependent: this signaling type takes place when we have two neighboring cells that are in a **direct contact**, **via plasma membrane proteins** contact directly as a ligand to the receptor binding with. **(Picture A)**

2-Via secreted signals:

- **Paracrine (local mediators):** via neurotransmitters and cytokines, action on adjacent target cells. **(Picture B)**
- **Synaptic:** via neurotransmitters, similar to paracrine between neuron that synapses with another neuron or target cell, the action on post-synaptic cell. **(Picture C)**
- **Endocrine:** via hormones, action on distant target cell **(Picture D)**
- **Autocrine:** via growth factors, action on the same cell (The cell releases the signal is also the target)

10) Types of signaling ligands

A. Ligands that bind to cell-surface receptors: **(They mostly can't cross plasma membrane)**

1. Neurotransmitters (NT), i.e. norepinephrine, histamine **(charged, polar)**
2. Peptide hormones (P), i.e. insulin **(large molecules)**
3. Growth factors (GF), i.e. NGF, EGF, PDGF **(large molecules)**
4. Lipophilic signaling molecules, i.e. prostaglandins **(charged)**

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.

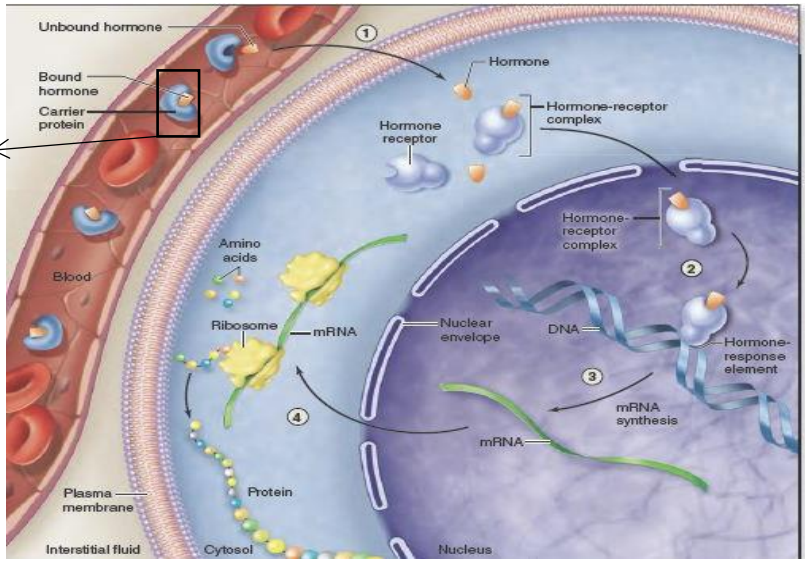
11) Chemical classes of hormones

A) Lipid soluble hormones:

- They can easily diffuse cross plasma membrane

- When they are transported in **PLASMA** (blood stream not plasma membrane) they have to use **transporting proteins** because they are lipophilic

Using transporter in PLASMA (blood stream)



EXAMPLES:

A) Steroid: Lipids derived from cholesterol **(lipophilic hormones)**.

❑Testosterone ❑Estradiol ❑Cortisol ❑Progesterone

B) Thyroid (amine but lipid soluble)

C) Nitric oxide (NO)

B) Water soluble hormones:

- When they are transported in **PLASMA** (blood stream) they transport in **"free"** form (don't need transporter protein)

EXAMPLES:

• 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), they are **charged** at physiological level so they are water soluble, they cannot cross the membrane by simple diffusion.

• 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.

Some books classify hormones polar/nonpolar

• Can gain entry into target cells.

• Steroid hormones and T_4 (thyrxine –tetraiodothyronine, which can pass through the plasma membrane)

THE END OF SHEET #16

سبحان الله والحمدلله ولا إله إلا الله والله أكبر

"لا يُستطاع العلم براحة الجسد"