Physiology
Sheet **No.**
13

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IMPORTANT DEFINITIONS !!

***SIGNALING*:** cell-cell communication via signals**.**

***SIGNAL TRANSDUCTION*:** process of converting extracellular signals into intracellular response without the physical ingress of the molecule to the cell. even if the ingression is done the message should be transferred via signaling pathways.

LIGAND: the signaling molecule, ex: hormones.

RECEPTOR: specific proteins that bind to specific ligands .they Transmit

signals to intracellular targets. Different

receptors can respond differently to the

same ligand.

COMPONENTS INVOLVED IN SIGNALING TRANSDUCTION:

1)LIGANDS : -they are located outside of the cell-, they are secreted from specific types of cells, in case of endocrine signaling they are secreted by GLANDS.

2)RECEPTORS : they are located on surface of the target cell.

Receptors and ligand work as a lock and key

3)INTRACELLULAR SIGNALING PROTEINS(mediatory proteins): interaction between different types of proteins Which in turn converts the signals into a response inside the cell. and includes the following:

A)intermediary proteins. B)enzymes (sometimes they participate in making second messenger. C)target protein. D)inactivating proteins.

NOTE: ligands are very important in determining the action that will result from binding of the ligand to a receptor .In addition, receptors play an important role in signaling pathways; sometimes ligands can bind to different types of receptors each one gives unique response according to the type of receptor that is used.

Overview of Signal Transduction

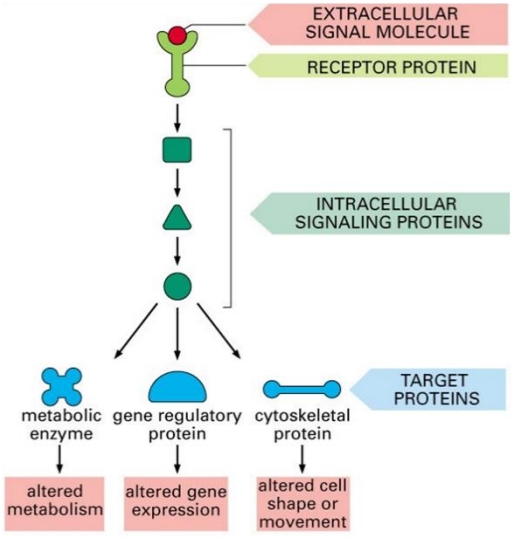


Figure 15–1. Molecular Biology of the Cell, 4th Edition.

-specific binding between the ligand and the Receptor leads to **changes in the receptor** which Transduce other proteins. Then, several **Interactions between proteins** In the cell until the Signal reaches the target.

-NOTE: The change/response happens To the target protein.

- For example:
- The **target** could be:
- •A **metabolic enzyme**, (inactive ⇨ active) which **alters** the **metabolism** in the cell.
- •A **gene regulatory protein**, which **alters gene expression**.
- •A **cytoskeletal protein**, which can transport an object from inside to outside the cell in variety of processes such as, **exocytosis , cell division and altering cell shape and movement**.

THE SCENARIO FOR SIGNALING:

1-a ligand will be secreted from a cell .

2-the ligand will bind to its specific receptor on the **surface of a neighbor cell** or a cell **at a Distance** from the secreting cell .

3-receptor-ligand binding will induce changes

In the receptor f.e: **a conformational change**,

Which in turn would induce other intracellular

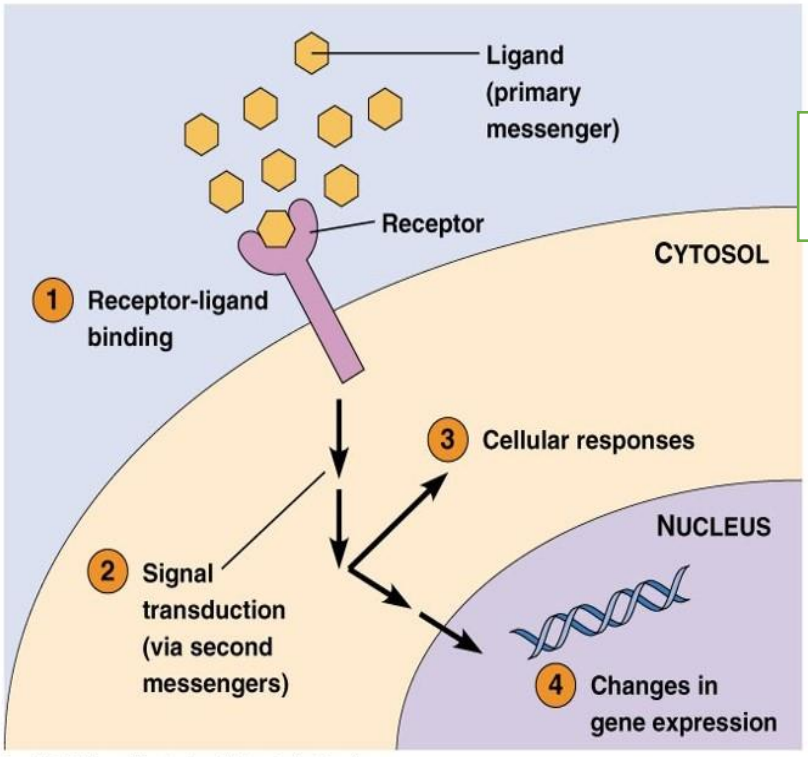
Proteins, one of which is the second messenger,

That will 1)induce **change in target proteins** to

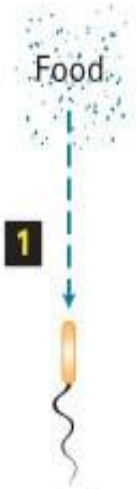
Induce cellular response. Or 2)- **the second messenger** will **go directly to the nucleus** and **induce changes in gene expression**.

So**, cell signaling** is a **complex (multi-step) process**, it is **NOT a one-way process** (one signal, one target). There could be **many stimuli** that cause **many responses in the cell.**

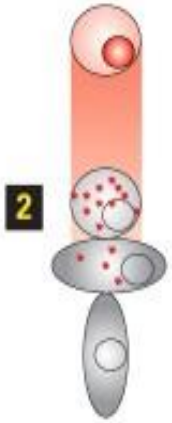
Signals get translated into cellular response **or changing in gene expression**



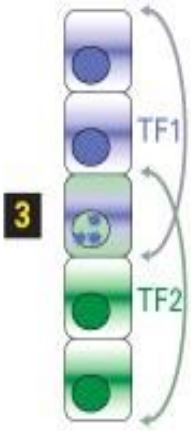
Signaling is responsible for how cells can respond to their environment and how they can differentiate



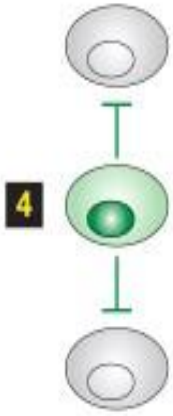
Cells adjust to their particular environmental inputs (e.g., oxygen, sugar, and temperature)



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 previous picture is in this page.(it will include what the doctor said to elaborate more).

-Each number will represent the number in the picture.

-Signaling is important for to maintain the life of a cell, why?

Because cells live in a **dynamic environment** (both external and internal), so cells must respond to changes in the surrounding environment to maintain **homeostasis**. And this response happens due to signaling between cells and the stimulus (changes in the environment).

-Functions of signaling:

1- Allows cells to respond to environmental changes such as : changes in temperature, in oxygen availability …etc.

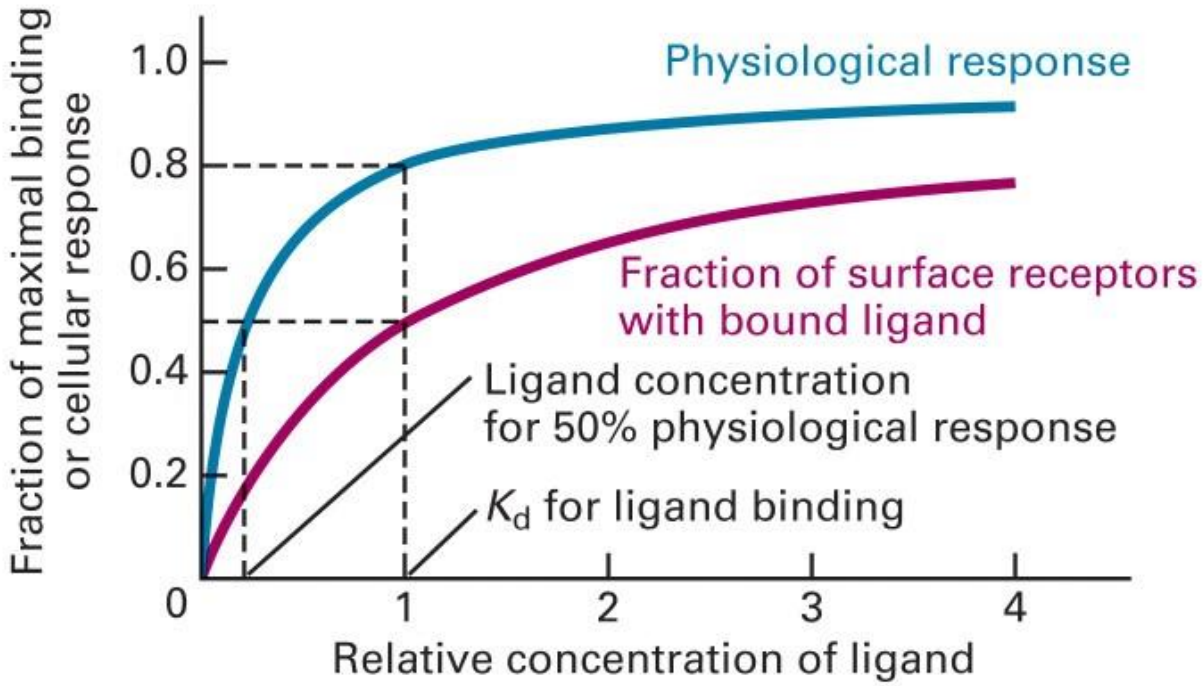
2- Signals **aren't on/off switchers**. sometimes we have **graded signals**, **Graded signals** cause(induce) cells to **differentiate** into different types of cells.(because different intensities of certain signals can have different effects on cells which causes differentiation) .

3- **combined signals** can cause **differentiation.**

4-Signals don't always stimulate(excite)... they can be **inhibitory,**

Signals that are inhibitory for a certain cell can stop or slow many mechanisms…f.e: duplication, proliferation..etc.

5- Different signals can integrate to help the cell to adjust to external changes or to act differently or to change with time(differentiation).



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

-If concentration of ligand =1 then **50% of receptors** will bind to their ligand and we will have **nearly maximal physiological response** (in the picture her it's almost **80%(0.8)**).

-If we **double** the concentration of the ligand so it becomes 2 this will induce **more binding** and we will get almost **65% of receptors** bound to their ligand so physiological response is almost **90%** now .

-So even at **lower concentration of ligands** (concentration 1 and 2), we were able to achieve a **very close to the maximal physiological response,** BUT when we increased the concentration of ligand from 1 to 2 the physiological response increased only 10%(from 80% to 90%).

SO WE DON'T NEED ALL THE RECEPTORS TO BE BOUND TO LIGANDS IN ORDER TO INDUCE A GOOD PHYSIOLOGICAL RESPONSE.

-Another reason why not all receptors are required to bound to ligands to induce a good physiological response is because **one signal can be amplified** (will be explained more in further pages).

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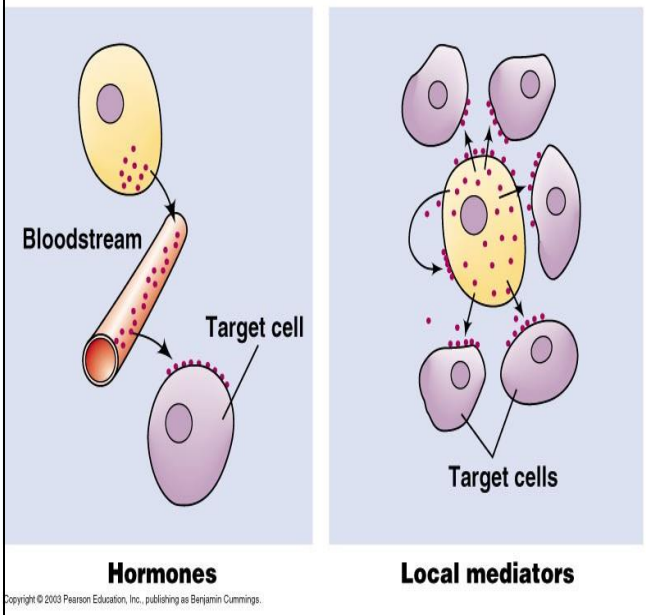
CHARCTARASTICS OD SIGNALS:-

1-SIGNALS CAN ACT LOCALLY OR AT A DISTANCE.



1-**signals can act locally** (at a short Distance or at the same secreting cell):

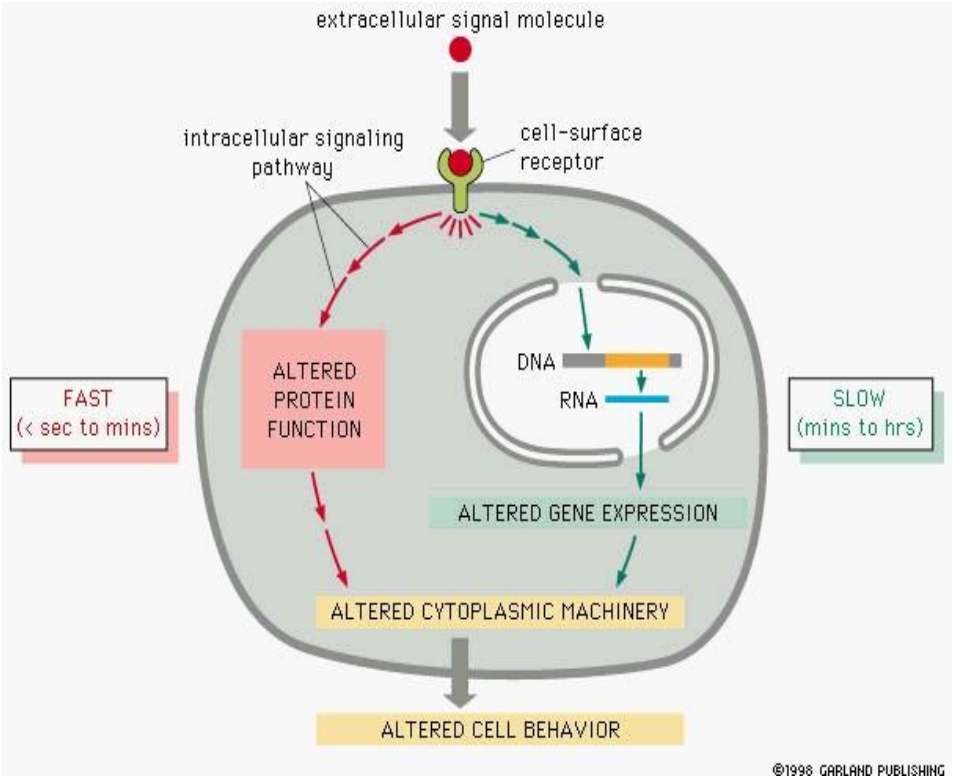
ligands secreted from a cell can bind to receptor on target cells (they are **neighbor** to the secreting cell) in this case the ligands are called **local mediators.**

2-**signals can act at a distance**:

Some ligands(like hormones) secreted from glands for example are transported **via blood(circulation)** into a distant Target cell.

DON'T LIMIT YOUR CHALLENGES , CHALLENGE YOUR LIMITS

2-RESPONSES CAN BE SLOW OR FAST



Responses can be **fast or slow** depending on the **responding cell** (depending on the **mechanism** induced**(by interactions between intracellular signaling molecules**) to make changes ***{gene expression takes longer than altering protein function***}

-when the ligand binds to the receptor the signal is transferred to the cell… now the **response** takes 2 scenarios **FAST** or **SLOW.**

FAST RESPONSE	SLOW RESPONSE
-Happens in **cytoplasm.** - An example: activation of A enzyme (it's **already there** in Cytoplasm) that will carry a Certain function within The cytoplasm like **Changing the shape** of a part of the cytoskeleton of a cell which will cause **binding of cytoskeletal** -*takes sec to few mins.*	– Happens in **nucleus.** - **signal** is **transduced** into the **nucleus**, where **gene expression is altered** (activation for gene expression of **certain** parts of a gene will be translated into RNA then protein. This will change cytoplasmic machinery (any organelle in cytoplasm) which will change cell Behavior(function). - Takes from **minutes to** *Hours maybe even days.*

3-Signals are amplified

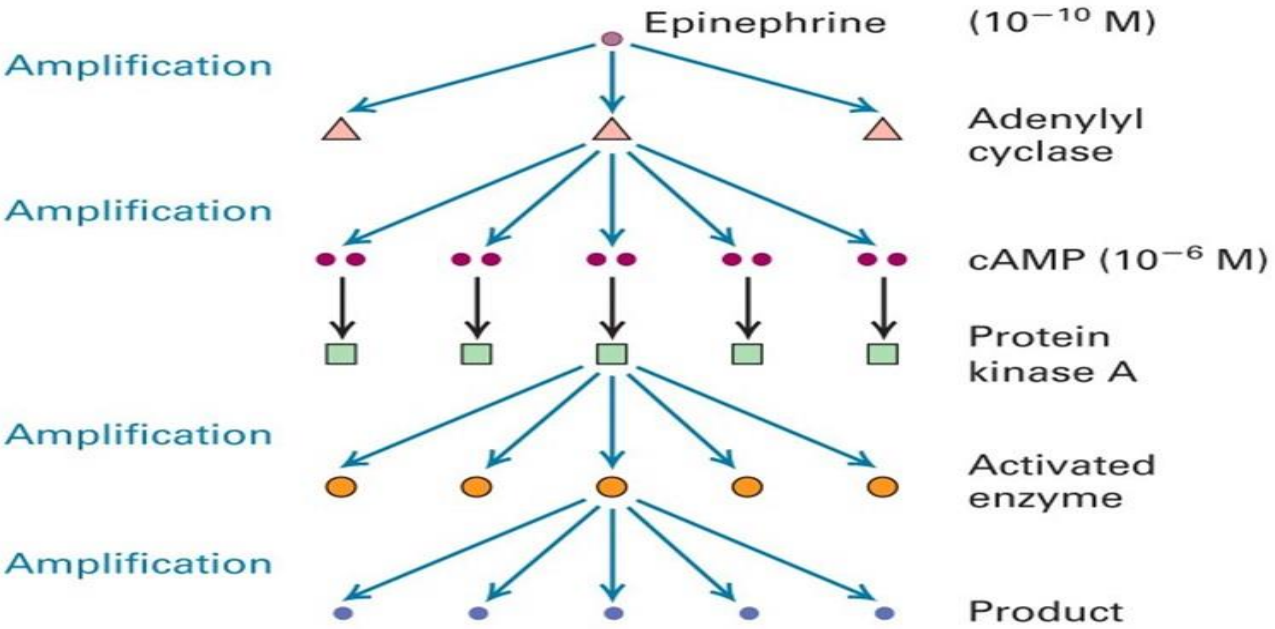
Why does a small concentration of bound ligand cause high physiological response? And why don't all of the receptors need to be bound?

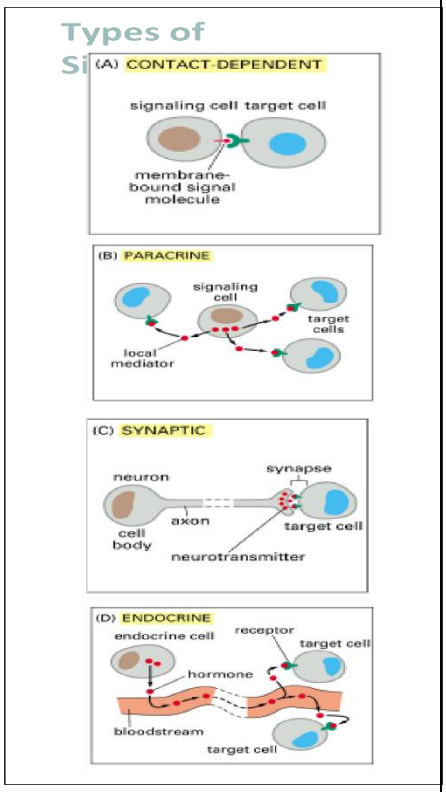
After explaining the mechanism of amplification we will reach the answer.

 As an example of amplification we have epinephrine (which is secreted from the adrenal medulla due to sympathetic stimulation) in the image for an example the concentration of epinephrine was (10^{-10}) Molar.

This epinephrine will bind to receptors that will activate an enzyme called adenylyl cyclase found on the cell membrane, note that one epinephrine was able to activate many adenylyl cyclases and each adenylyl cyclase will generate cyclic AMP (cAMP) with a concentration of (10^{-6}) Molar because of the many adenylyl cyclase that were activated.

 Each cAMP will bind to an enzyme called protein kinase A and each protein kinase will activate many enzymes, at the end with each step the signal was amplified drastically.





TYPES OF SIGNALING:

1) **Contact-dependent-via proteins in PM:** the adjacent cells are very close to each other,and they are connected together by intermediate receptor.(picture A)
2) **Via secreted signals:**
   a) **Autocrine:** via growth factors, cells that releases the signal is the target.
   b) **Paracrine:** via neurotransmitters and cytokines, action on adjacent target cells.(picture B)
   c) **Endocrine:** via hormones , action on distant target cells,* circulating in blood stream*,(picture D)
   d) **Synaptic:** via neurotransmitters, action on post synaptic response to electrical stimuli

e) Types of signaling ligands:

1) Ligands that bind to cell-surface receptors:

A)Neurotransmitters (NT), i.e. norepinephrine,histamine hydrophilic (charged, polar),they cant ebter the cell because they are polar charged molecules> they bind to the surface to convey their message

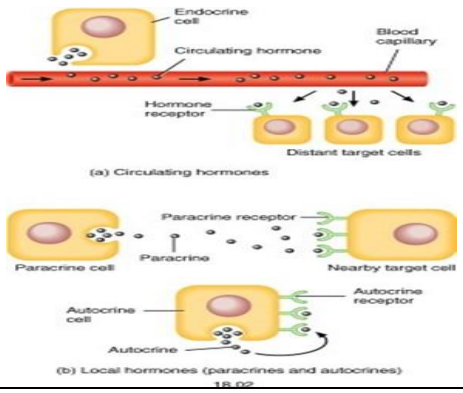
B) Peptide hormones (P), i.e. insulin - can't cross membrane(large molecules).

C) Growth factors (GF), i.e. NGF, EGF, PDGF (charged molecules)

D) Lipophilic signaling molecules, i.e. prostaglandins (lipophilic = soluble in lipids).

2) 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**.**



Local vs circulating hormones :

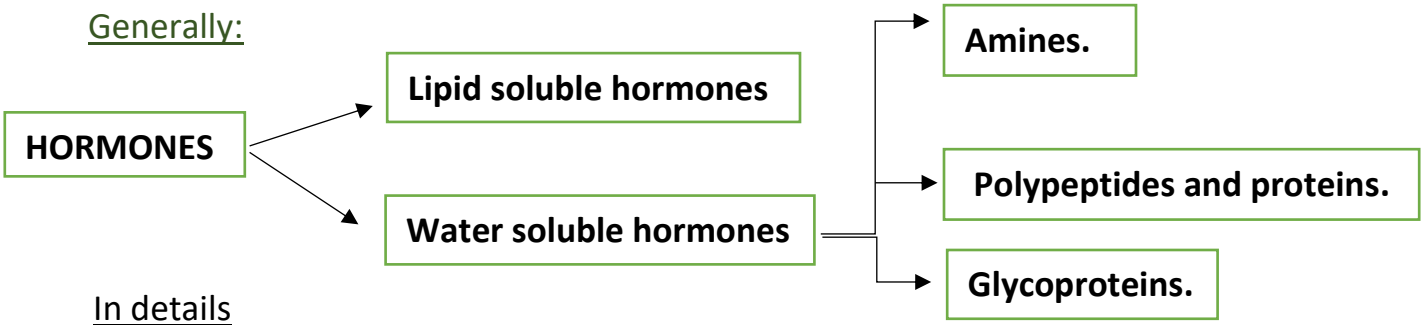
Local hormones :paracrine and autocrine signals (usually used to maintain homeostasis especially by negative feedback).

Circulating hormones : endocrine signals (via blood stream for long distance to arrive the target cells

NOTE:it is very important to now the chemical classification of hormones to determine the accurate signaling mechanism that will occur.

CHEMICAL CLASSIFICATION OF HORMONES:

Generally:



In details

HORMONES → **POLAR:** H_2O soluble.

NON-POLAR(LIPOPHILIC):H_2O insoluble .

*can gain entry into target cells.

*steroid hormones and T_4 (thyroxin-tetraiodothyronine)

HORMONES

PROHORMONES: precursor is a longer chained polypeptides that is cut and spliced to make the hormone.

E.g: proinsuline > gives insulin.

PREPROHORMONES: prohormones derived from larger precursor molecule. Eg: preporinsuline.

PREHORMONES: molecules secreted by endocrine glands that are inactive until charged into hormones by target cells.

inactive hormones> active hormones /eg: T_4 converted to T_3.

Explanation about pro and prepro hormones:

The pancreas does not produce insulin directly but rather produces it in a form of preproinsuline , then they are cut to proinsuline ,which are broken down into smaller parts to arrive at its original insulin formula.

PREPROINSULINE > PORINSULINE > INSULINE

Chemical classes of hormones according to their solubility in water or lipids (more details for the first diagram above):

- **LIPID SOULABLE HORMONES:**
  - they can easily cross the plasma membrane and bind to their targets.
  - They use transport proteins in PLASMA, why? Because they are hydrophobic materials so they require an assistant to carry them through bloodstream, which is mainly water.
  - Examples:
    - ✓ Steroids: lipids derived from cholesterol(lipophilic hormones)
    - ✓ Testosterone
    - ✓ Estradiol
    - ✓ Cortisol
    - ✓ Progesterone
    - ✓ Thyroid (amine but lipid soluble)
    - ✓ Nitric oxide (NO) : Due to its gaseous nature, it easily penetrates the plasma membrane
- WATER SOLUBLE HORMONES: hydrophilic materials so they don't need transport proteins in their movement through blood stream. But the cant cross plasma membrane.
  - **AMINES:** hormones derived from tyrosine and tryptophan.
  - **POLYPEPTIDES AND PROTEINS:**
    - ✓ **Polypeptides:** chains of < 100 amino acid length eg: ADH
    - ✓ **Protein hormones:** polypeptide chains > 100 amino acid eg: growth hormones.
  - **EICOSANOIDS(PROSTAGLANDUNS):** local mediators derived from arachidonic acid-20 carbon 4 double bonds. In physiological level they are charged molecules so the cant enter inside the cell.
  - **GLYCOPROTEINS:**
    - Long polypeptides >100 bound to 1 or more carbohydrate (CHO) groups.
    - They have alpha and beta subunits (alpha is common and beta is specific)
    - ✓ FSH,LH,TSH and hCG (human chorionic gonadotropin).

The End

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