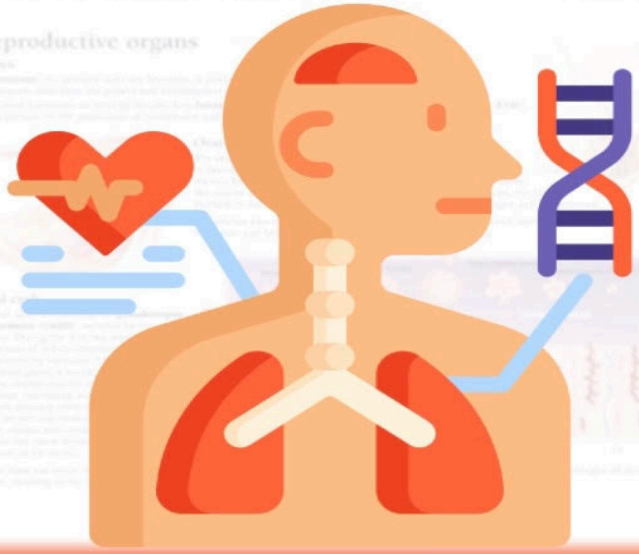
Doctor 022

Physiology

Sheet no.



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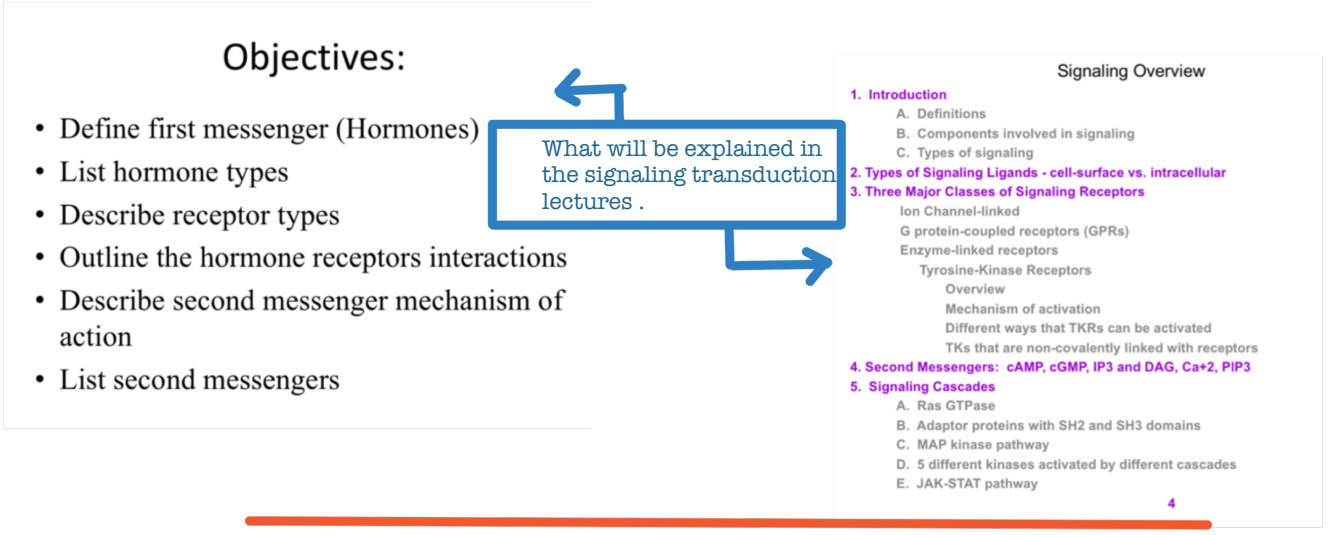
The first lecture in signal transduction

An overview of what we will learn during these lectures :

We will define different mechanisms for signaling transduction and this actually to understand the way of ligand to induce their effects in our body .
The scope of these lectures is to understand the mechanism for ligand actions ,different types of ligand in terms of chemical structure .
We will describe many receptor types and their interactions also we will know what we mean by second messengers that are used by different hormones in order to induce their effects .



What we mean by signaling ?

Cell -cell communication via signals .

Signal transduction :

Process of converting extracellular signals into intra-cellular responses .

Ligand:

The signaling molecule .

Receptors :

Specific protein that bind specific ligand on its binding site in order to transmit signals to intracellular targets **Different receptors can respond differently to the same ligand .
If the ligand binds to more than one type of receptor ,we will find different actions ,because actions depends not only on the ligand but also in the receptor .

Component involved in signaling :

1-Ligands
2 -Receptores
3-intracellular signaling proteins
4-intermediary proteins
5-Enzymes
Which induce different metabolic activities in the cell
6-second messengers
7-target proteins
8-inactivating proteins

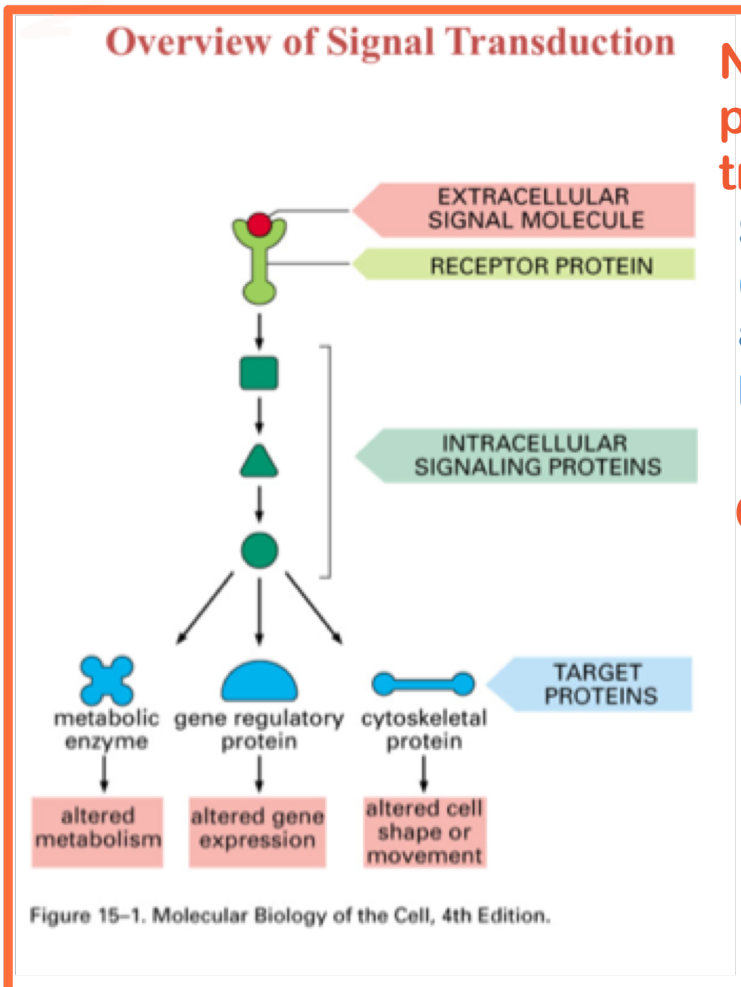


Figure 15–1. Molecular Biology of the Cell, 4th Edition.

Note that we have a set of protein involved in signaling transduction :

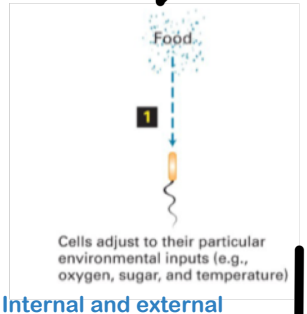
Starting from ligand (signal) ,receptors that bind ligand and other intracellular signaling proteins involved .

Over view of signal transduction

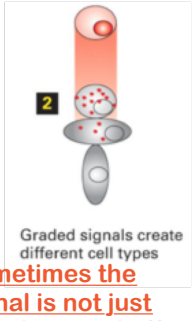
We have ligand ,recptor , different signaling proteins (mediators to transmit signal) these mediators could be sesond messenger and at the end we have target proteins .

Target protein could be an activity of an enzyme or it could be a gene regulatory protein (in order to change the expression of a certain gene) or it could be a cytoskeletal protein that will change the structure of the protein or maybe the movement and shape of the cell .

The main functions of signaling

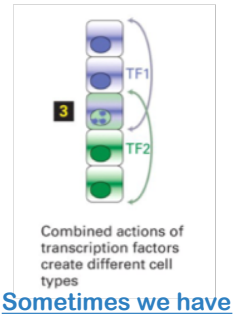


Internal and external environment in the cell is always changing so the cell must respond to these changes in order to maintain homeostasis ,so cells try to adjust to their environment and that happens due to signaling between stimuli& between the cells [this is the way cells can detect and respond to their environmental changes ,such as in oxygen availability ,sugar availability or in temperature .

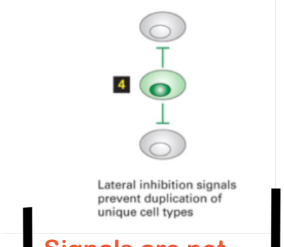


Sometimes the signal is not just switch on and off but also we have graded signals which may induce cells to differentiate into different types of cells ,there are so many different types of signaling that can take place *different intensities of certain signal can have different outcomes or different effects on cell and that what we may see in the differentiation of cells

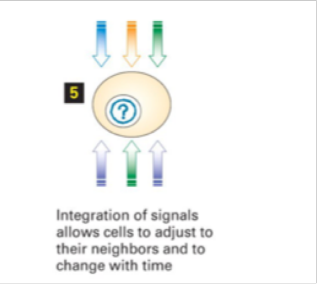
ممكن شدة الـ signal تأثر على نوع الخلية المتمايزة .



Sometimes we have combined actions of different signals and factors can create different cell type (and that is also we see in differentiation) so we are not talking about one signal per cell,we are talking about a group combination of signals that have different actions and different effects on transcription factors •so different combination can create different type of cells and also important for cell differentiation

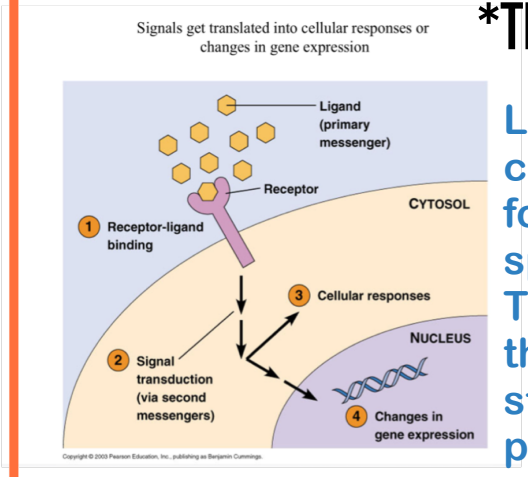


Signals are not always excitatory ,it can be inhibitory for a certain cell maybe stop duplication or stop proliferation



Different signals integrate and then together can help the cell to adjust to some external changes to the external environment or to act differently or change with time

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



*The main mechanism for cell signaling *

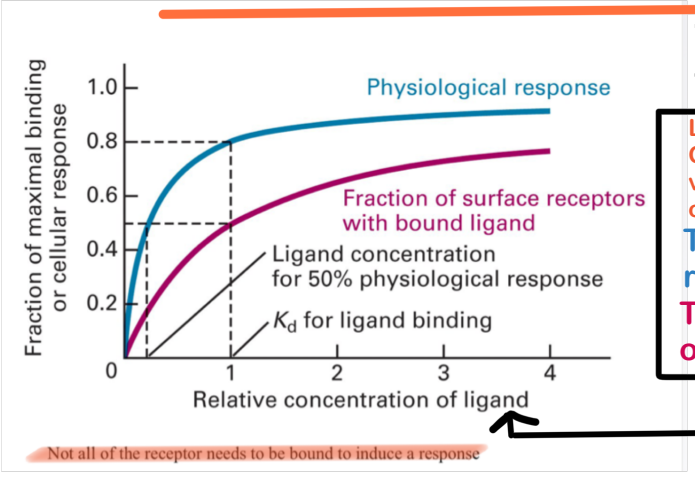
Ligand was secreted by maybe hormone secreting cells(gland) .This ligand will find a specific receptor for maybe on the neighboring cell and bind with this specific receptor .
This receptor -ligand binding will induce changes in the receptor such as conformational change in the structure of the receptor which will induce other proteins that can bind to the receptor inside the cell .

So the binding of the ligand transduced changes at the intracellular level ,and these changes will be transduced into different target protein in the cell ,and these mediators we can call it second messenger .

Second messenger transduce these changes into a cellular response ,increasing activity of a certain enzyme or substance -producing a certain product,it could directly go to the nucleus to induce changes in the gene expression and in production of receptors or enzymes or different proteins (structural proteins).

As you can see here signals that are outside the cell are translated into cellular response ,and without having even to transport this signaling molecule into the cell that is what we call is **Transduction**

We don't necessarily need to transport the molecule itself into the cell to induce its actions ,only binding to the receptor can induce these actions .



The question now is,do we need all receptors to be bound to their ligand in order to have a certain physiological response ?

Look at this graph
On x-axis we have the relative concentration of a ligand which is normal values of concentration .And on y-axis the fraction of maximal binding or cellular response .
The first curve which demonstrate the physiological response it could be like a contraction of a muscle .
The second curve which demonstrates the fraction of surface receptors that are bound with their ligand

محتويات الشكل :

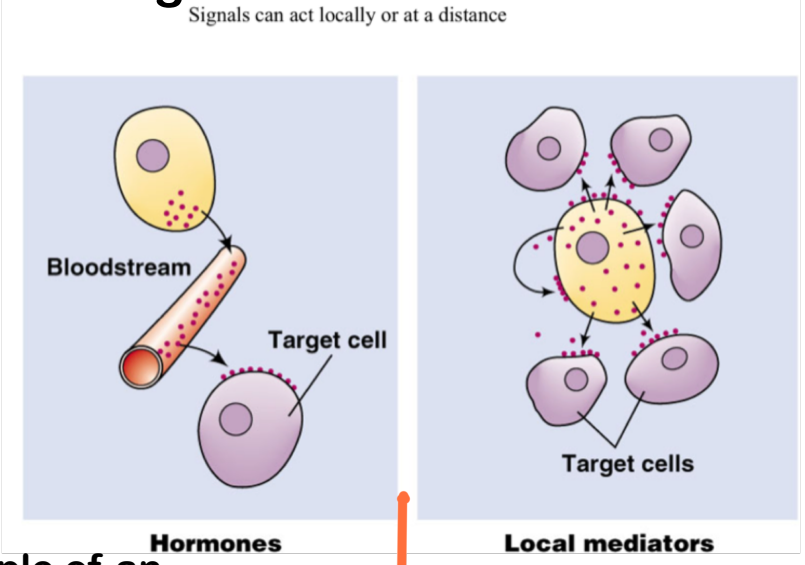
We will explain why [Not all of the receptor need to be bound to induce a response].

Let's see how the fraction of surface receptors bound to the ligand relative to the physiological response . Take the first concentration which is a normal concentration of a ligand .You can see even with 50%of a receptors bound to their ligand we can have ,close to maximal physiological response which is 0.8 or 80% .However we have 50% of the receptors occupied or bound to the receptor .

When we look at the double concentration of the ligand ,it induces more binding,so we will get about 70% or 65% of the receptors that bound to their ligand ,the physiological response is about 90%.

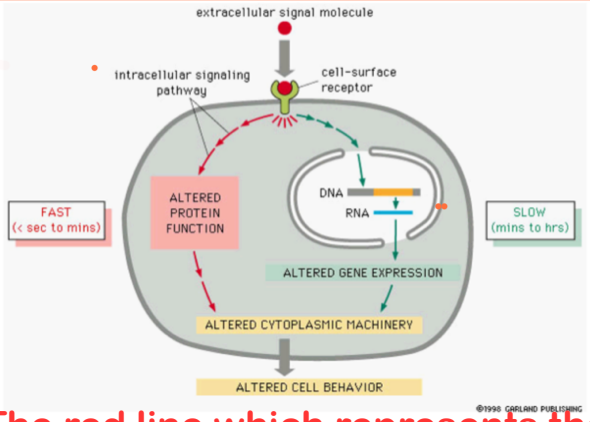
Notice that
At low concentration of ligand ,we achieve a response close to the maximal physiological response .And even when we doubled the concentration ,we did not get much increase in maximal physiological response (increasing in less than 10%) .We don't need to have all receptors bound to their ligands in order to induce a good response .

* Another characteristic of signals that signals can act locally or at a long distance from the secreting cell.



Another example of an signal ,sometimes signals are secreted by secreting cell or gland and then are transported via blood or through the circulation into a distant target cell .
Example : a hormone was secreted by pituitary gland(in the brain) and this signal (hormone) has to be transported or carried by the blood to go to a distant target such as ,muscle cell or bone cell in lower limb musceles and must know that endocrine hormones use this way for signaling via blood without ducts.That's why it called the endocrine (having no duct) .

on the right ,we have this example of signal secreted by a cell and the target is binding to the neighboring cell's receptors ,so the signal acted locally through a short distance from the secreting cells and then bound to receptors on the target cell which is very close to the screting cells In this case we call this signals local mediators.



Responses can be fast or slow depending on the root or mechanism that used to make a response

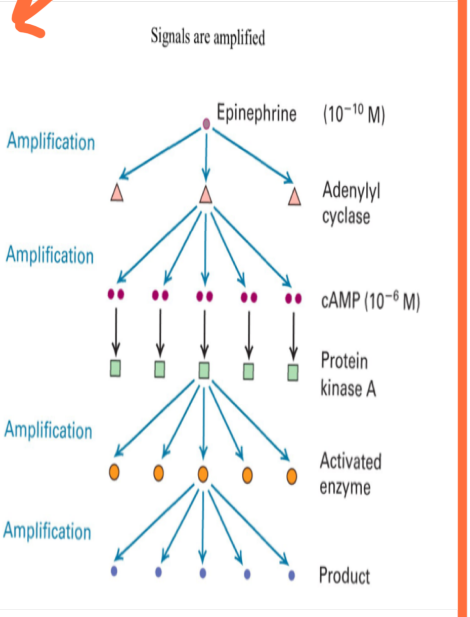
We have the typical signaling molecule that binds to a cell surface receptor .Look at the downstream signalings.

The red line which represents the altered protein function (for example activation of a certain enzyme and the response maybe will be changing the shape of cytoskeleton inside the cell and the result is changing in cell behavior this is fast response (the duration can be from second to minutes)already we have proteins and we only change interaction between them .

The second Scenario is that the signal is transduced into the nucleus where gene expression now is modified ,like activation of the expression of a certain part of a gene that will be translated into RNAand then into a generation of a new proteins or peptides that will change the cytoplasmic machinery (any organell in the cytoplasm) which induce a change in the cell behavior or function ,that actually is slow because it takes minutes to hours or days in order to get these changes .

The signal has the ability to be amplified

شرح الرسمة :

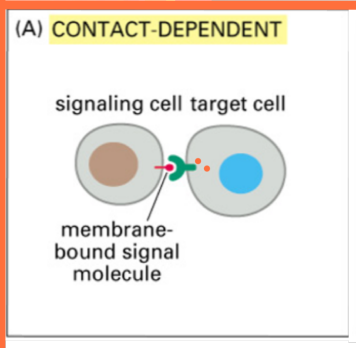


For example we have epinephrine that was secreted from the adrenal medulla due to sympathetic nervous stimulation (in stress).The concentration of epinephrine was 10^-10 molar (less than nanomolar).This epinephrine will bind to receptors that will activate an enzyme called adenylyl cyclase.this concentration of the epinephrine activated many adenylyl cyclases ---Each one of these adenylyl cyclases will generate cAMP (the concentration of cAMP is 10^-6 ,so the concentration is increased --Each cAMP will bind to an enzyme called protein kinase A which have the ability to phosphorylate and activate many enzymes .So by the end of signaling cascade ,we end up having the signal amplified and aggravated .

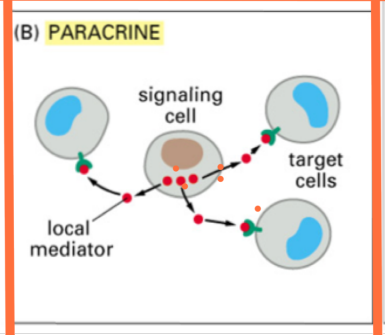
Now we can answer the question of do we need all receptors to be bound to their signals in order to have a good affair a physiological response ? No,because signals are amplified

even if we have a very low concentration of a ligand we will amplified these ligands as a second messengers or amplified many enzymes to induce response

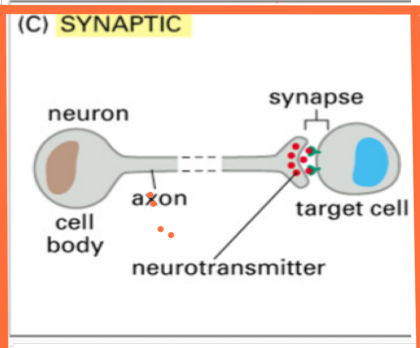
5 Types of signaling



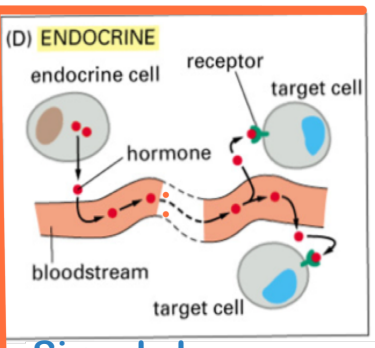
The two neighboring cells are in direct contact via binding of plasma protein .



The cell secretes a signal that travel short distance ,binding on neighboring cell's receptors and signals that use this type of signaling known as local mediators or local factors .



It's nearly similar to paracrine but the main difference in this type that we have a synapse between cells and the type of cells is neurons ,so the neurotransmitters (signal) cross the axon and bind to the other neuron of ligand target channel via synapse



Signals here called hormone and this hormone which is secreted from endocrine cell or gland can transport to a distant target cell via blood stream e.g: pituitary gland as we mentioned before

And the last type of signaling is autocrine , when a secreted signal binds to the receptors on the same secreting cells.meaning that I have the signal and receptor on the same cell.Usually this type of signal is considered as a feedback of the cell .how ? When cell secretes a signal ,this signal maybe bind on the receptors on the same cell (which secreted a signal)to inhibit the cell (negative feedback).

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

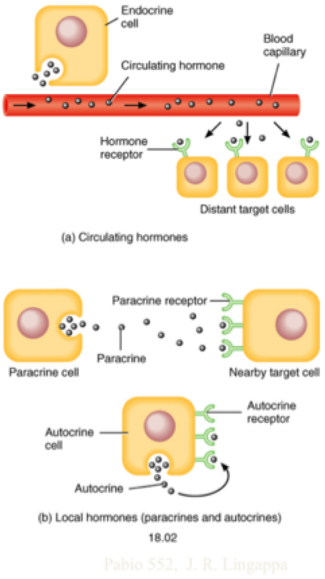
The cell surface receptors are integral proteins cross the cell membane through extracellular domain ,and this extacellular domain has a specific binding site , these ligands has a characteristc that they charged polar (they cannot cross the plasma membrane) or peptides (large also cannot cross) So usually these ligand cannot cross the membrane (even some lipophilic signaling molecule has charge so they can't cross the membrane without receptors)

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.

They can freely cross the plasma membrane by simple diffusion and then interact with intracellular receptors on the cytosol or sometimes even to the nucleus

Local vs. Circulating hormones



As we discussed previously there are two types of hormones :

1-Hormones that affect locally which we call it paracrine or autocrine ,so their target cells are present locally very close to the secreting cells or (same cell will be affected in autocrine) .

2-circulating hormones "Endocrine hormones "when the signaling molecules travel via the blood circulation and then affect the distant target cell .

Let's look at the chemical classifications of hormones .Hormones are divided into either lipid soluble or lipid insoluble hormones .

****For the lipid soluble hormones** Use transport proteins in the plasma

They can easily diffuse across the plasma membrane such as steroids .However in the plasma when they are transported,they have to use transporting proteins because they are lipophilic they don't like the media of plasma which is water mainly .When they reach their target ,they can diffuse across the plasma membrane .

Examples :

1- steroid → Lipids derived from cholesterol and all types of steroids are lipophilic hormones

A-testosterone.

B-estradiol

C-cortisol

d-progesterone

2-Thyroid (amine but lipid soluble).

3-Nitric oxide(NO)is a gas and also highly permeable

**The water soluble hormones or in other terms the lipid insoluble hormones

These actually circulate freely in the plasma ,they are free form in the plasma (free from tansport proteins) .

Examples :

1- Amines

hormones derived from tyrosine &tryptophan .

2-polypeptides

Chains of <100 amino acids in length such as ADH(antidiuretic hormone)

3-protein hormones

Polypeptide chains with >100 amino acids like growth hormone

4-Eicosanoid (Prostaglandins)derived from arachidonic acid(20carbon 4double bonds).

They are Lipophilic,usually they found charged at a physiological PH (considered water soluble) so they cannot cross plasma membrane by simple diffusion .

Chemical Classification of Hormones

- Glycoproteins:
  - Long polypeptides (>100) bound to 1 or more carbohydrate (CHO) groups.
  - Examples : FSH and LH, TSH and hCG (human chorionic gonadotropin)
  - They have α and β subunits (α is common and β is specific)

*All of the lipophilic or hydrophilic hormones are glycoproteins

FSH~follicle stimulating hormone
LH~luteinizing hormone
TSH~thyroid stimulating hormone

- Hormones can also be divided into:
  - Polar:
    - H_20 soluble. Hydrophilic
  - Nonpolar (lipophilic):
    - H_20 insoluble.
      - Can gain entry into target cells.
      - Steroid hormones and T_4 (thyrxine –tetraiodothyronine))

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يعطيكم العافية ...
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