◉Sheet ○Slides

Number

16

Done by:

Daniah Ahmad

Corrected by:

Bushra Haddad

Doctor

Eba'a Alzayadneh

Cell signaling: cell-cell communication via signals.

Signal transduction: the process of converting extracellular signals into an intra-cellular target that will perform an action or make a response in the cell.

☆ Extracellular stimulus will cause changes in intracellular processes.

☆ There are series of events (cascade of interactions) occurring between proteins and molecules which produce the response.

☆ Sometimes, there could be different receptors for the same ligand which causes different responses. So, the response doesn't depend only on the type of the ligand, but also on the type of the receptor that mediates (transduces) these changes as it will transport the message from the signaling molecule to the downstream molecules.

In conclusion, different receptors can respond differently to the same ligand.

Components involved in signaling:

•Ligand: The signaling molecule.

•Receptors: Bind specific ligands and transmit signals to an intracellular target.

•Intermediary proteins(intracellular signaling proteins): transport the message to the target.

•Enzymes: could be the target or the intermediary protein which activates other proteins.

•Second messengers.

•Target proteins.

•Inactivating proteins: to stop signal transduction.

About the figure below:

-Specific binding between the ligand and the receptor leads to changes in the receptor which transduce another protein. Then, several interactions between proteins in the cell until the signal reaches the target.

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

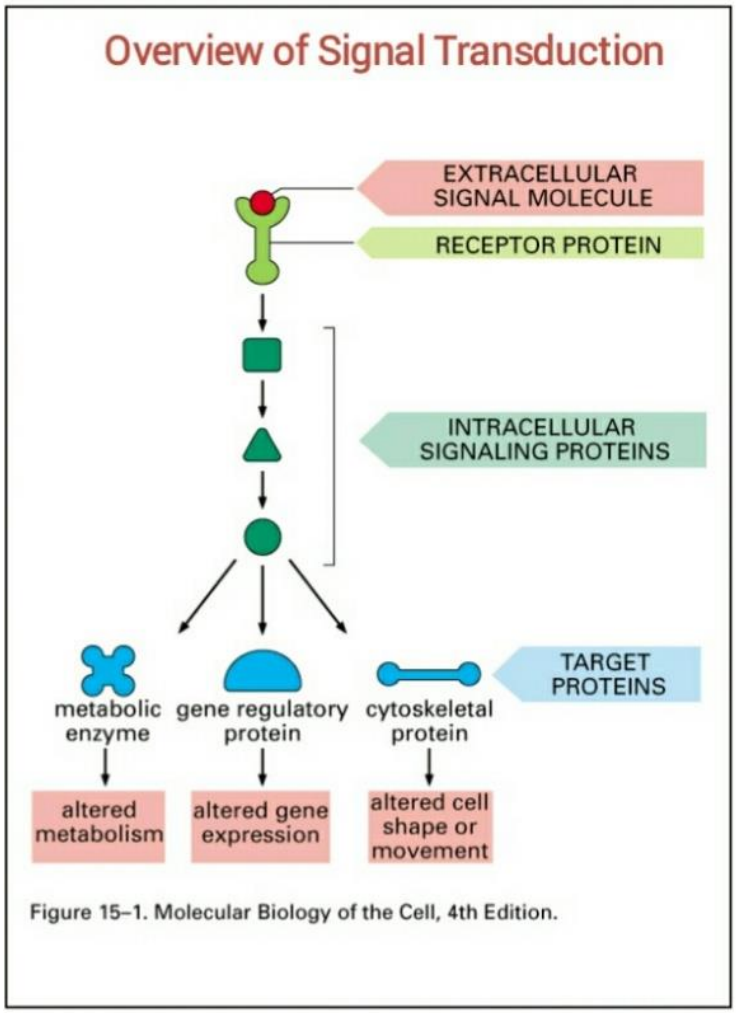
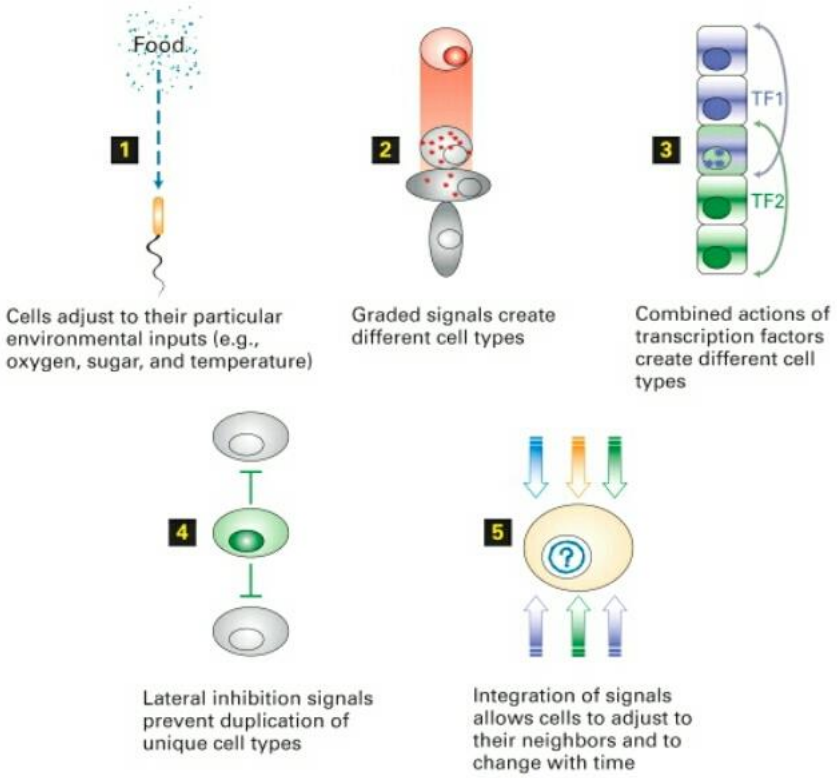


Figure 15–1. Molecular Biology of the Cell, 4th Edition.

movement.

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.

The results of signal transduction:



1) Response to environmental changes around it

The cell should respond to any change in the availability of food e.g. sugar , oxygen, temperature by adjusting the activities inside the cell to maintain life (homeostasis).

-It may change its metabolic activity.

For instance , if there is a deficiency in glucose, the cell takes in a subsequent signal concerning this deficiency. As a result, it should produce glucose from alternative sources.

2) Response could be graded i.e. several responses could happen due to different strengths of signaling molecules.

-In the figure above, it's about cell differentiation.

⇨ The cells which receive large amounts of signaling molecules differentiate into a specific type of cells . Other cells which receive lower amounts differentiate into another type of cells , while cells that don't receive anything differentiate into a third type of cells.

☆This increases the complexity of the responses from the same signaling molecule.

3) Combination of stimuli

TF: Transcription Factor

E.g. TF1 is a signaling molecule that causes the cell to become a specific type of cells, TF2 produces another type of cells . However, if the cell is effected by both TF's, it will produce a third type of cells.

This will cause integration of stimuli to produce specific response.

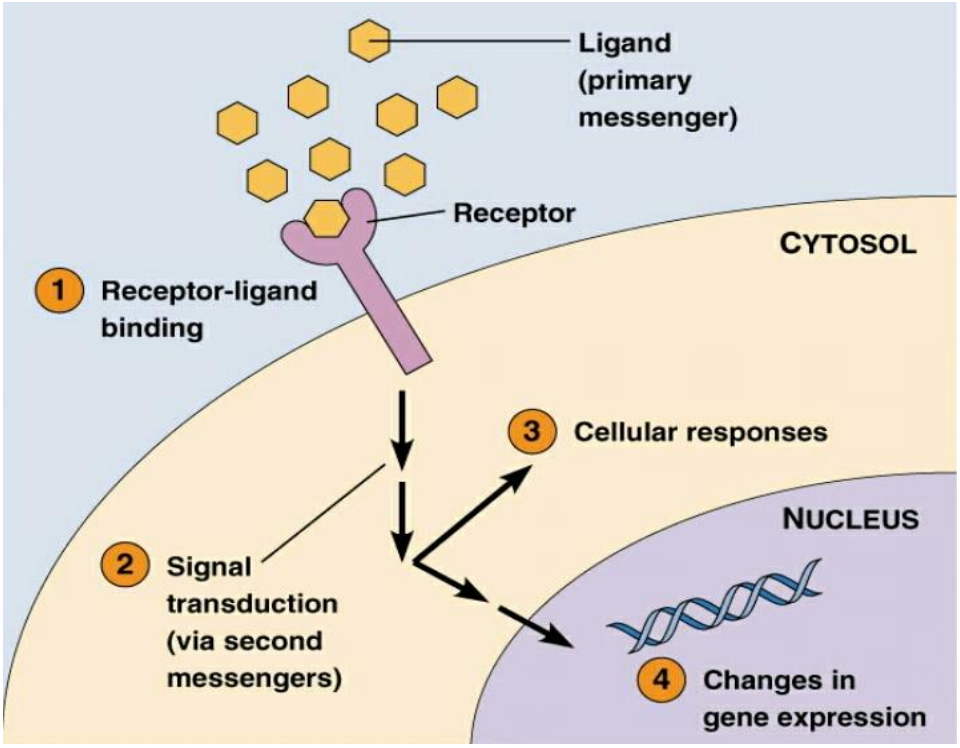
4) Stimuli could be inhibitory

E.g. Certain signals may stimulate cell proliferation (excitatory). Other signals may inhibit cell proliferation (inhibitory).

○●

The classical view about cell signaling:

-It is not the only view



A receptor on the membrane binds to a ligand (primary messenger) , which is the hormone. This will induce a change in the receptor, which may be transduced to other intermediary proteins (inside the cell).

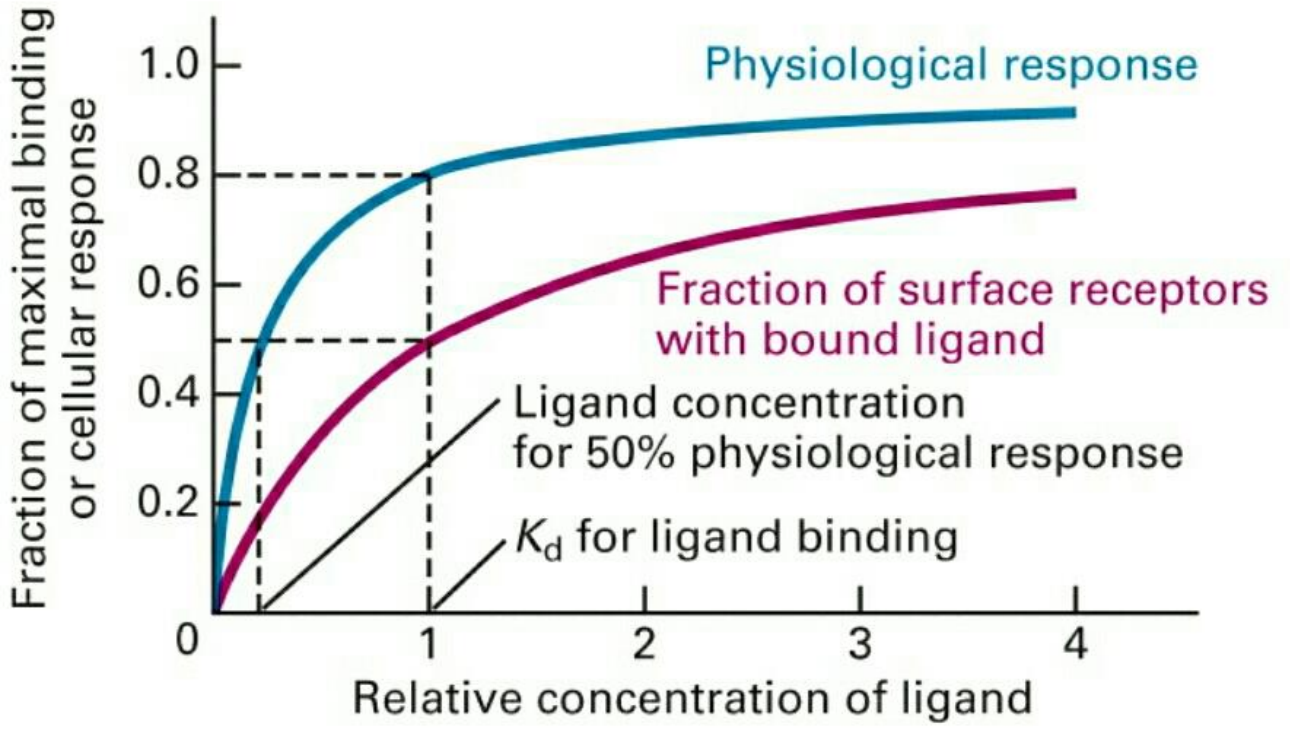
Now, there are two ways to complete the response:

1) These proteins will interact with other proteins (cascade of events) and a second messenger may be produced which effects the target protein (activation, deactivation), this will affect the function of the cell, or produce a new function.

2) These intermediary proteins may enter the nucleus and change the gene expression to induce or inhibit the production of a particular type of proteins This will also change the cell's function. **This type of response needs a longer time.**

☆Do we need to saturate all the receptors to have the physiological response that we need?

No we don't need that, the following figure will explain:



We have 2 curves:

The lower one shows the percentage of the membrane receptors that will be bound to the ligand when a specific concentration of ligand molecules is available.

The upper one shows the maximal physiological response that will be obtained when a specific concentration of ligand molecules is available (as a percentage).

Now, let's take an explanatory example

X axis shows the relative concentration of a particular ligand (e.g. Ach)

1=normal (regular) concentration(2)= Double concentration, (3)= triple concentration,(4)= quadruple concentration.

Measuring the response is done either by recording the physiological response (e.g. muscle contraction), or by measuring the percentage of ligands bound to the receptors.

⇨ If the concentration of the **receptors** that bounded to ligands is 1: 50%, we will obtain 80% muscle contraction which is sufficient.

⇨ If the concentration of the receptors that bounded to ligands is 2: 60% , we will obtain 90% muscle contraction.

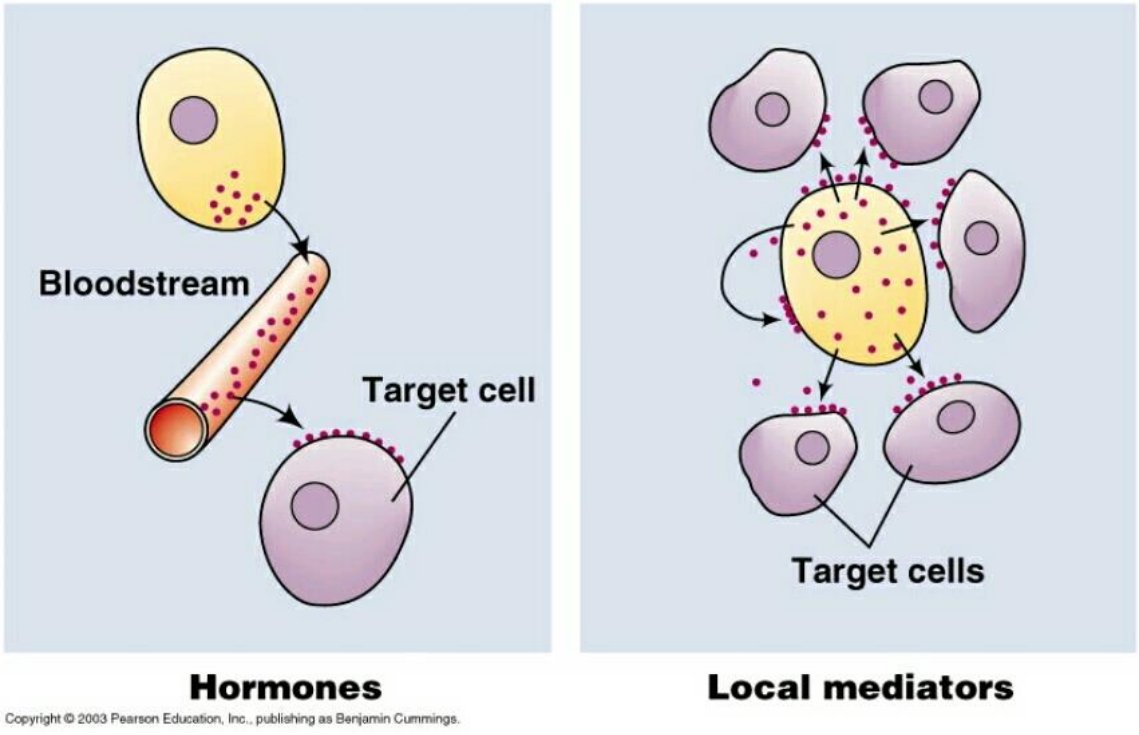
So, it isn't necessary to saturate the receptors to obtain sufficient physiological response.

★But how could this occur?

Although just 50% of the receptors are bounded to ligands the response is amplified inside the cell to have 80% physiological response.

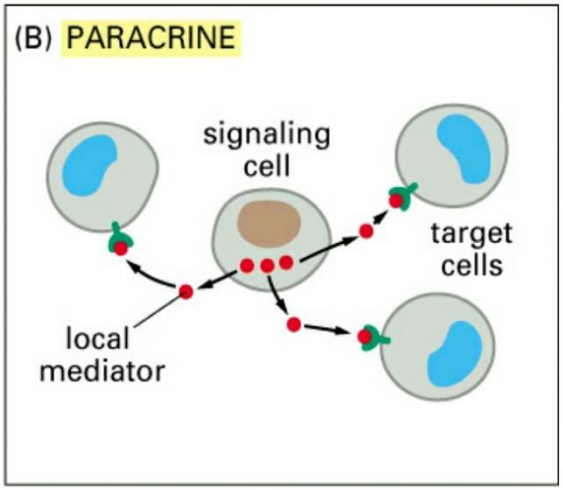
K_d will be discussed later.

Main types of cell signaling:



1) Local Mediators

Paracrine: the cell secretes signaling molecules, then these molecules bind to nearby (neighboring, adjacent) cells. (signaling molecules are either neurotransmitters or cytokines.)



Autocrine: The cell secretes signaling molecules, then these molecules bind to its own receptors i.e. cells that release signals are also considered targets.

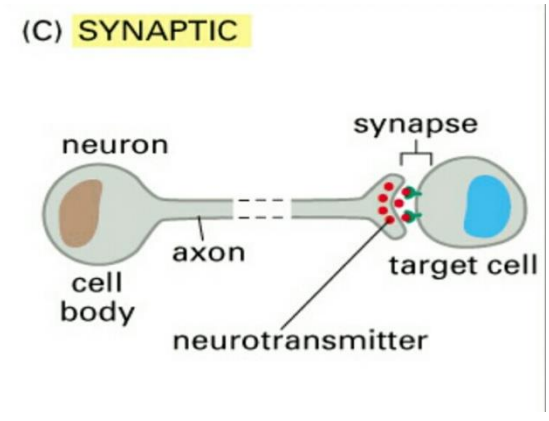
This type could be used:

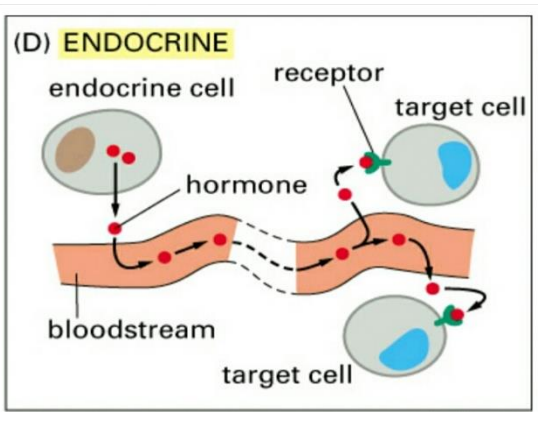
-When the cell secretes growth factors and the cell itself needs growth.

-For feedback, to tell the cell that the amount of secretion is enough now and inhibit secretion (negative feedback), or stimulate more secretion (positive feedback).

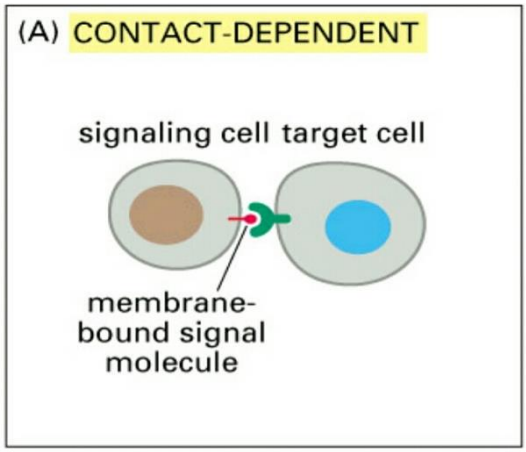
2)Endocrine: Via hormones i.e. secretory cells secrete ligands (endocrine hormones), these ligands are carried via the blood to reach distant cells. Then, they bind to their receptors and induce signal transduction inside the cell.

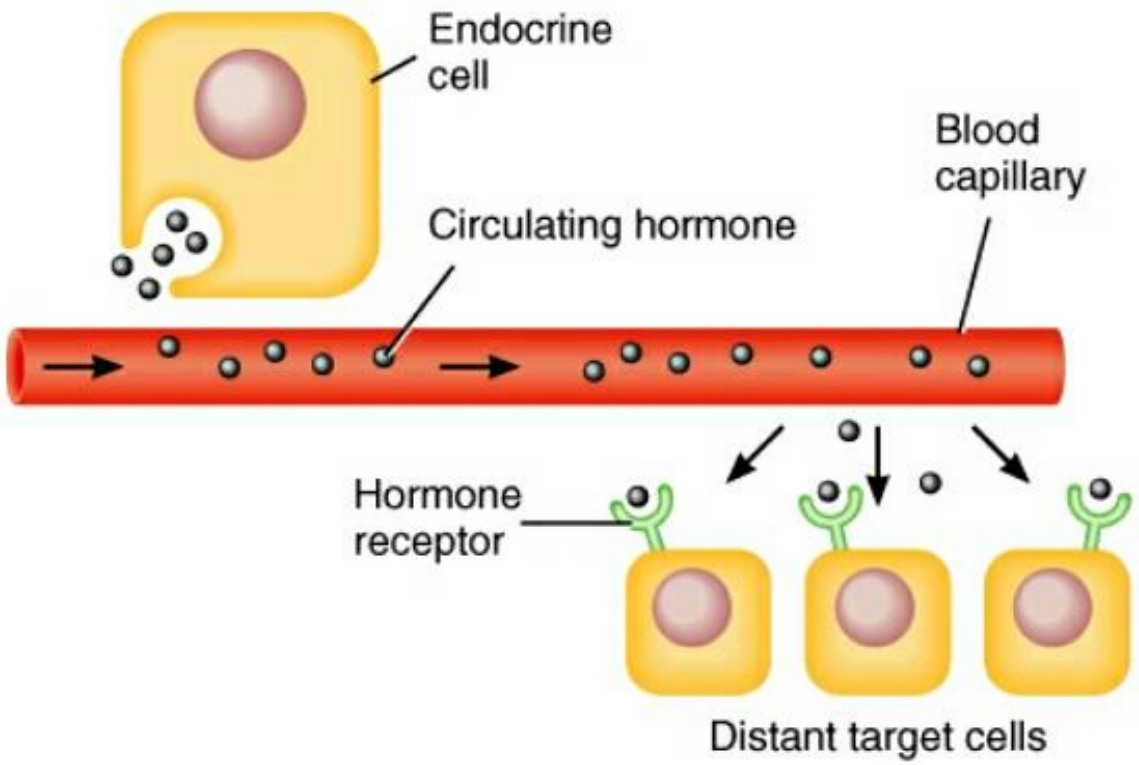
3)Synaptic: Via neurotransmitters i.e. action potential on post-synaptic cell in response to electrical stimuli.



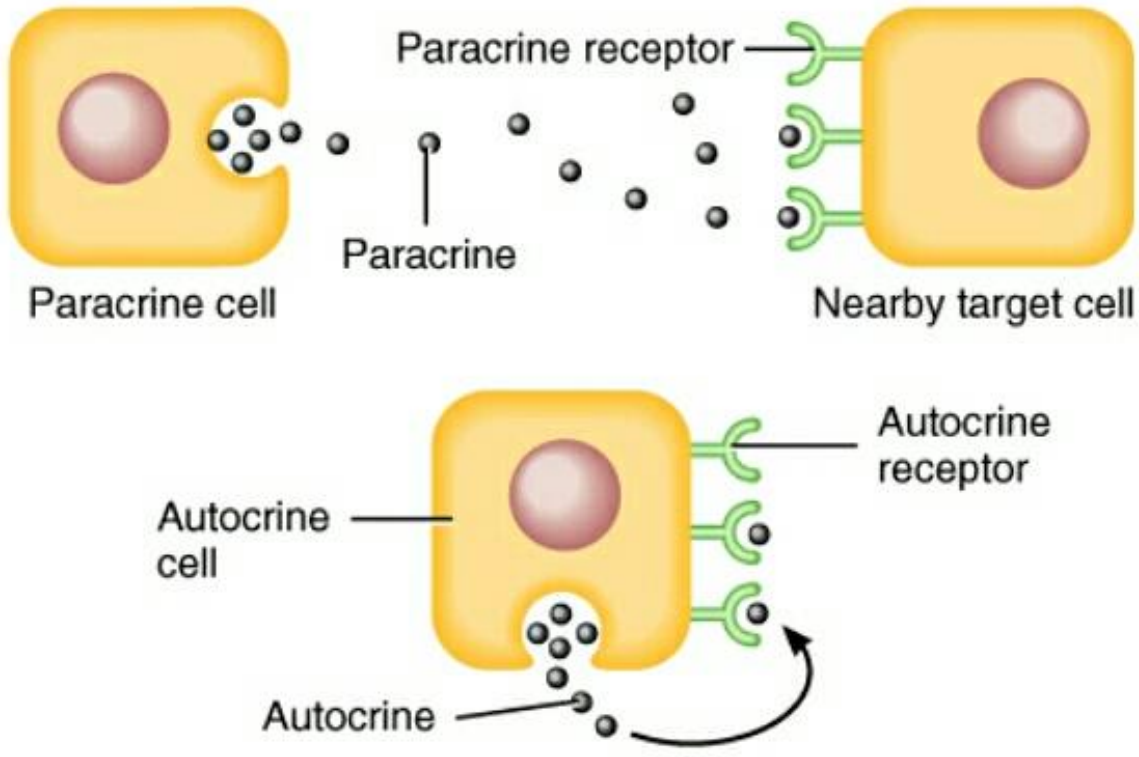


4)Contact-dependent: The ligand exists on the membrane of one cell. This ligand binds to the receptor on the membrane of another cell (these two cells must be in contact).



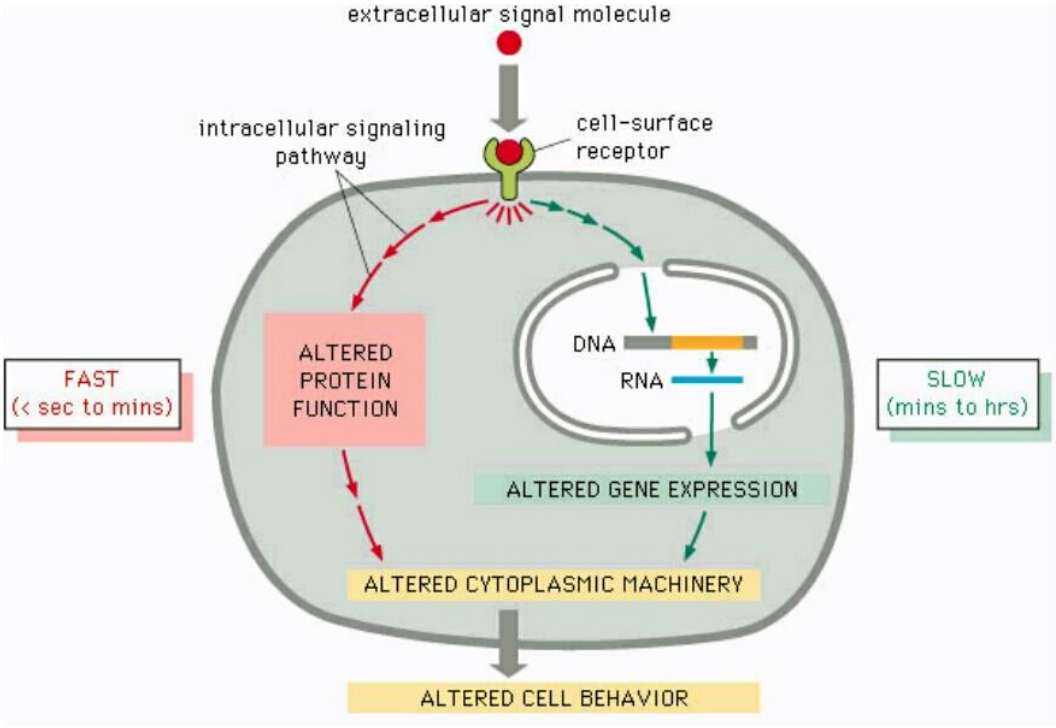


(a) Circulating hormones



(b) Local hormones (paracrines and autocrines)

Response could be slow or fast



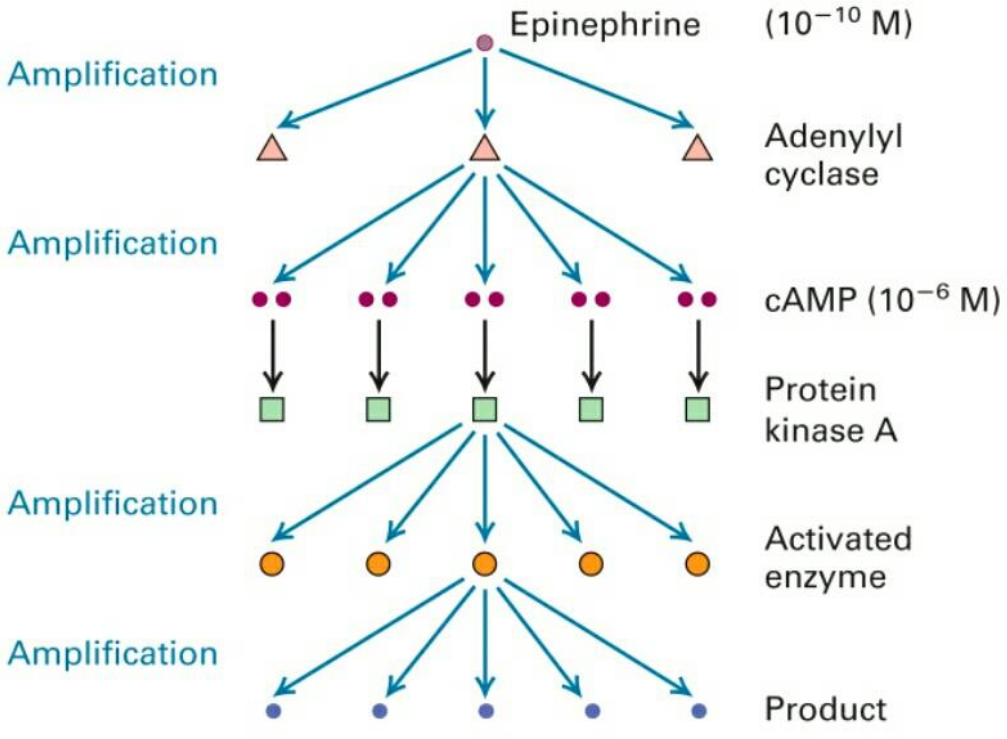
Fast ⇨Occurs within seconds or minutes. This is resulted in **alteration** in protein function such as,

Enzyme (on, off).

Cytoskeleton (induce movement of a vesicle).

Slow ⇨ Gene expression which causes synthesis of new proteins (include modifications + transport).

Amplification of signals:



We have a very small concentration of epinephrine (10^{-10} molar) , this small amount is able to activate several receptors (adrenergic receptors). This causes activation of an enzyme (adenylyl cyclase), which causes the production of a second messenger (cAMP) with a larger concentration than the concentration of the first messenger (10^{-6} molar) . The (cAMP) will cause several activation on several proteins in the cell (protein kinase A) .Now , several protein kinases are activated from a single adenylyl cyclase .Finally , we will finish with a larger (amplified) effect.

Types of signaling molecules:

The ligand could bind either with a receptor on the cell membrane, or inside the cell. This depends on the permeability of the membrane . So, the two categories of signaling molecules are :

1) <u>Ligands that bind to the intracellular receptors:</u>

●The membrane is permeable to these molecules (lipid soluble).

●They CAN bind to intracellular receptors (this is NOT the only way to transduce their message).

For example; steroids, thyroxine, retinoic acid and nitric oxide.

2) Ligands that bind to cell surface receptors:

●The membrane is impermeable to these molecules (not necessarily).

● The ONLY way to transduce their message is binding to cell surface receptors.

a) Neurotransmitters (NT): norepinephrine, histamine (hydrophilic, charged, polar).

b) Peptides (P): insulin.

c) Growth Factors (GF): NGF, EGP, PDGF.

d) Lipophilic signaling molecules: prostaglandins.

Classification of hormones according to the chemical structure:

⇨ **Lipid** *soluble hormones:* They are able to pass across the plasma membrane, but if they need to be transported via the blood, they are hydrophobic. So, they need transporting proteins (binding proteins) to reach the target cell.

They include:

1) Steroids: Lipids derived from cholesterol.

-Testosterone.

- Progesterone.

- Cortisol.

- Estradiol.

2) Thyroid Hormones: Especially thyroxine (amine but lipid soluble).

3) Nitric Oxide (NO)

Water soluble hormones: They are transported freely without the need of transporter proteins .

1) Amines: Hormones derived from tyrosine and tryptophan.

2) Polypeptides and Proteins:

- Polypeptides: Chains <100 amino acids in length such as, ADH.

- Protein Hormones: Chains >100 amino acids such as, Growth hormones.

3) Eicosanoid: Prostaglandins derived from arachidonic acid (20 carbons with 4 double bonds).

4) Glycoproteins: Long polypeptide >100 bound to 1 or more carbohydrate (CHO) groups, these hormones have α and β subunits (α is common and β is specific).

Such as; FSH, LH, TSH, hCG (human chorionic gonadotropin).

Hormones can also be divided into:

1) Polar: Water soluble.

2)Nonpolar(lipophilic): Insoluble in water.

Can gain entry into target cells.

Such as, Steroid hormones and T4 (thyroxine –tetraiodothyronine)

Note: A big thank to Basil Twal for helping in correction, I owe you!

Believe you can and you're halfway there.

-Theodore Roosevelt