بِسْمِ اللَّهِ الرَّحْمَٰنِ الرَّحِيمِ

PHYSIOLOGY

وَلَقَدْ خَلَقْنَا الْإِنسَانَ وَنَعْلَمُ مَا تُوَسْوِسُ بِهِ نَفْسُهُ ۖ وَنَحْنُ أَقْرَبُ إِلَيْهِ مِنْ حَبْلِ الْوَرِيدِ

Final | Lecture 4

Receptors Function & Signal Transduction L2

Written by : Jana Sawafta
Amal Al-khatib

Reviewed by : Rand Alkhateeb

Color coding used in the modified:

- *Black: the original slides*
- *Blue: the doctor's explanation/words*
- *Gray: additional information and explanation*
- *Red: important information*

Receptors Functions and Signal Transduction L2

Faisal I. Mohammed, MD, PhD

University of Jordan

Hormone Activity

depends on two main factors:
- [hormone]
- amount of present receptors on the target cells.

- Hormones affect only specific target tissues with specific receptors (the specificity of the hormone)
- Receptors are dynamic and constantly synthesized and broken down
  - Down-regulation- **decrease in receptor number** or **response** may be due to internalization of receptors (The receptors move from the cell surface into the cell (this is called internalization). Mostly for hormones that circulate almost all the time)
  - Up-regulation- **increase in receptor number** or **activity**, may be due to externalization of receptors or synthesis of new receptors. (Small amount of hormones → increase number of receptors to increase the affinity → better effect)

Effects of hormone concentration on Tissue Response

- **Priming effect (up-regulation):** (a hormone won't work unless another hormone acts before it)
  - Increase number of receptors formed on target cells in response to particular hormone. **Cortisol** causes a priming effect to increase the synthesis of **estrogen receptors**
  - Greater response by the target cell.
- **Desensitization (down-regulation):**
  - Prolonged exposure to high [polypeptide hormone].
    - Subsequent exposure to the same [hormone] produces less response.(Internalization of the receptor be phosphorylation)
      - Decrease in number of receptors on target cells.
        - Insulin in adipose cells.
  - **Pulsatile** secretion may **prevent or decrease** down-regulation.

as it controls the timing of hormone release. For example, cortisol is usually released in the morning and decreases in the afternoon

Effects of [Hormone] on Tissue Response

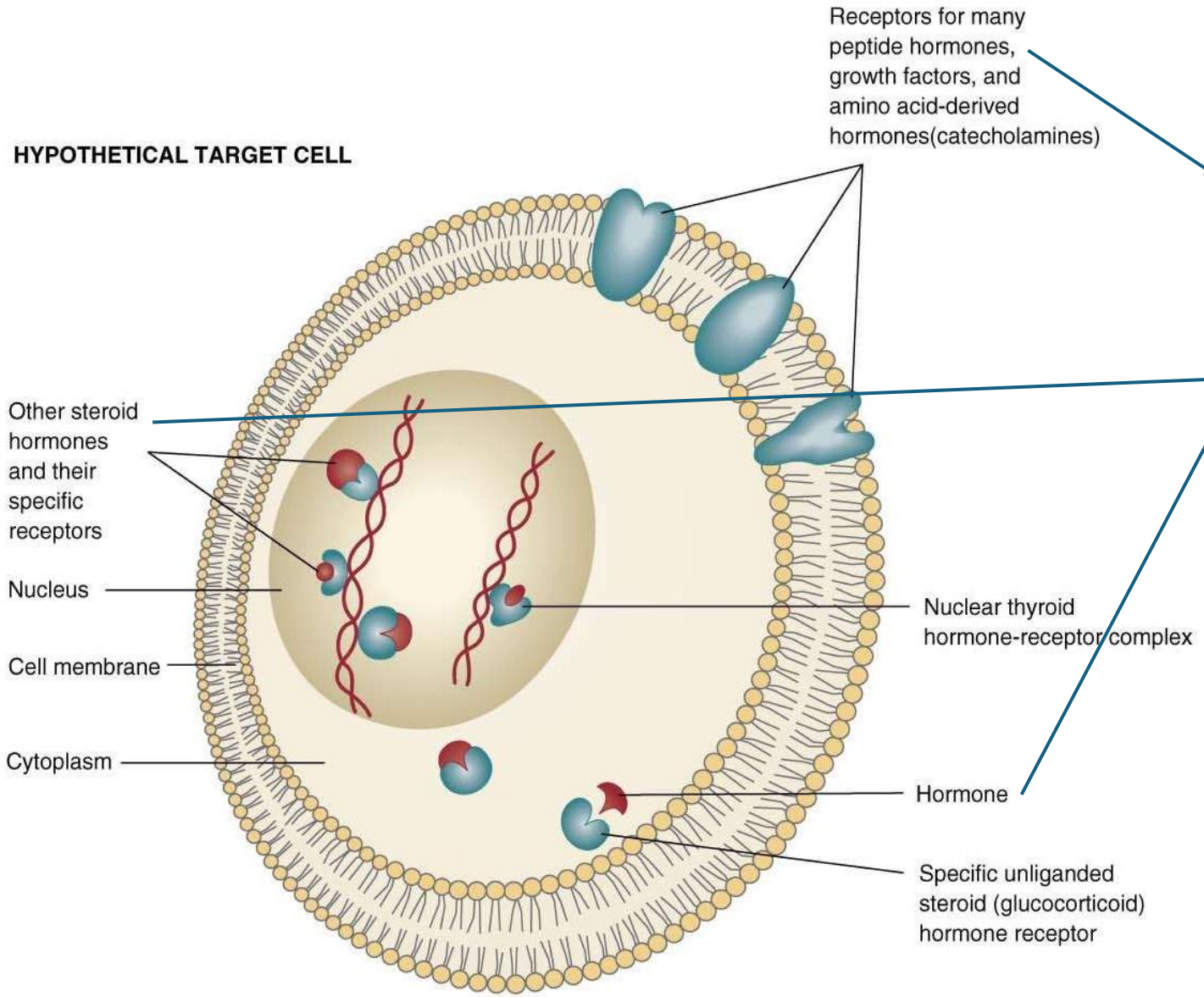
- [Hormone] in blood reflects the rate of secretion.
- Half-life:
  - Time required for the blood [hormone] to be reduced to ½ reference level.
    - Minutes to days.
- Normal tissue responses are produced only when [hormone] are present within physiological range.
- Varying [hormone] within normal, physiological range can affect the responsiveness of target cells.

There are two perspectives to consider: **pharmacology** and **physiology**.
Pharmacology deals with drugs and their effects.
Physiology, on the other hand, focuses on normal body functions and processes.
The previous two points are talking regarding to physiology

The half-life of a drug is important in pharmacology because it determines **how often** the drug should be administered. If a drug has a short half-life, it is eliminated quickly from the body, so it must be given more frequently (for example, two or three times per day). If it has a long half-life, it remains in the circulation for a longer time, so it can be given less frequently, such as once daily.

Peptide hormones (proteins) generally have a shorter half-life because they are easily broken down in the blood. In contrast, **lipid-soluble hormones** usually have a longer half-life because they are transported in the blood by **carrier proteins**.

For example, **thyroid hormone (thyroxine, T4)** is **lipid-soluble** circulates by carrier, which gives it a relatively long half-life compared to many peptide hormones. (7 days)



. Diagram showing the different locations of classes of hormone receptors expressed by a target cell.

Classification of hormones according to the location of their receptors.

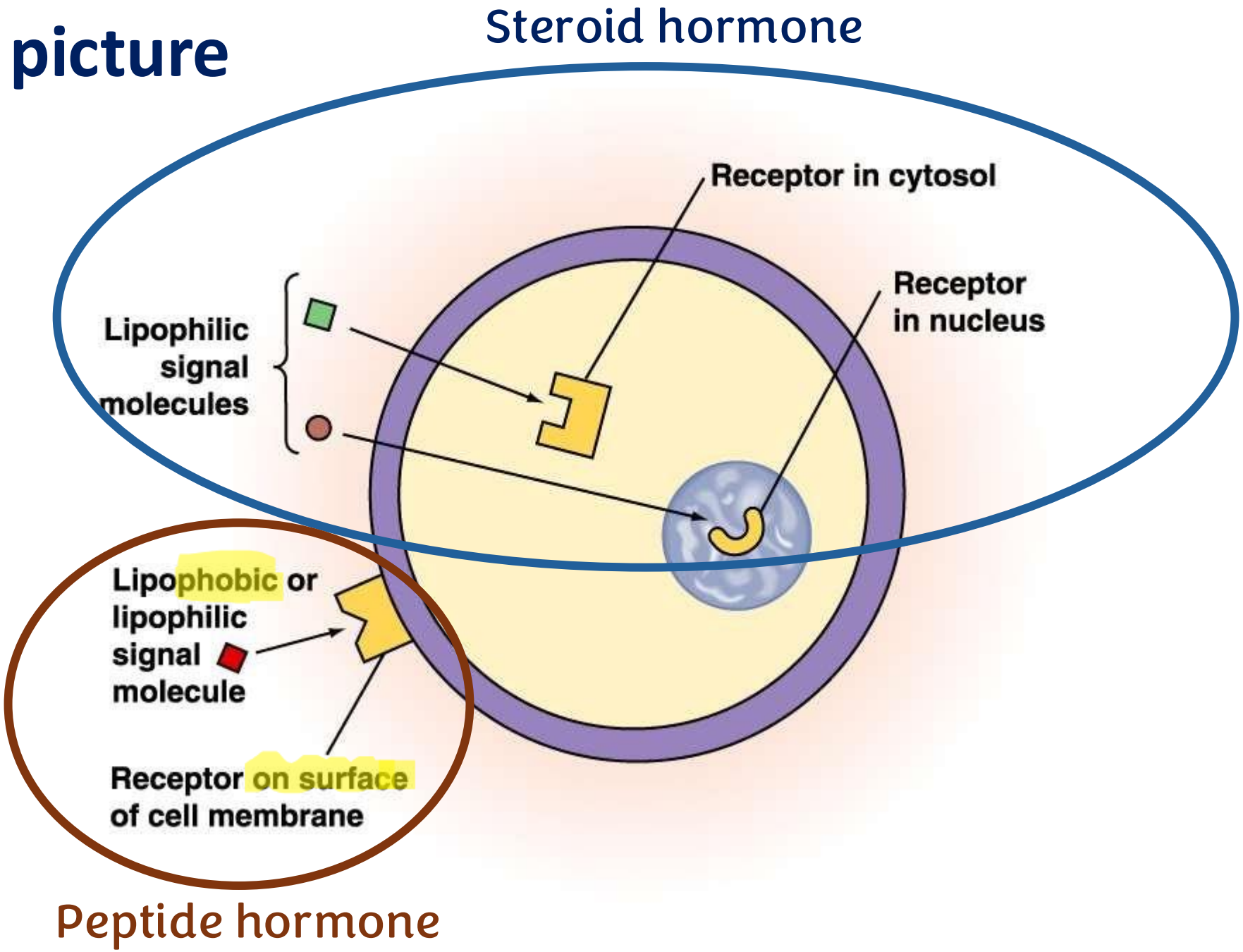
· **peptide hormones** : bind to receptors on the cell membrane because they cannot pass through the lipid bilayer.

· **steroid hormones** : diffuse through the phospholipid bilayer of the cell membrane and bind to intracellular receptors, either in the cytoplasm or in the nucleus.

- When the hormone-receptor complex acts in the nucleus, it influences gene expression and protein synthesis, that's why this mechanism is often referred to as a **genomic effect (related to genes).**

- However, some steroid hormones can also produce non-genomic effects. These non-genomic actions are usually mediated by membrane-associated receptors, these receptors are less common.

Another picture



Mechanisms of Hormone Action

- Hormones of same chemical class have similar mechanisms of action.
  - Similarities include:
    - Location of cellular receptor proteins depends on the chemical nature of the hormone. (lipid or water soluble)
    - Events that occur in the target cells. (second messenger mechanism (different ligands, but same mechanisms))
- To respond to a hormone:
  - Target cell must have specific receptors for that hormone (**specificity**).
    - Hormones exhibit:
      - Affinity (bind to receptors with high bond strength) high affinity means that we need small amount to act. While low affinity means that we need a large amount of the hormone to act, the **affinity** is measured by **K.m or K.d (half maximal effect)**
      - Saturation (low capacity of receptors). It is limited by the number of receptors (Vmax)

Mechanisms of Hormone Action

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

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 Or protein (integral or peripheral)

ligand

A small molecule that binds specifically to a larger one; for example, a hormone is the ligand for its specific protein receptor.

- **Membrane receptors**

  Membrane Glycoprotein or proteins

- **Intracellular receptors**

  - **Cytosol or nuclei**
  - **DNA binding protein**

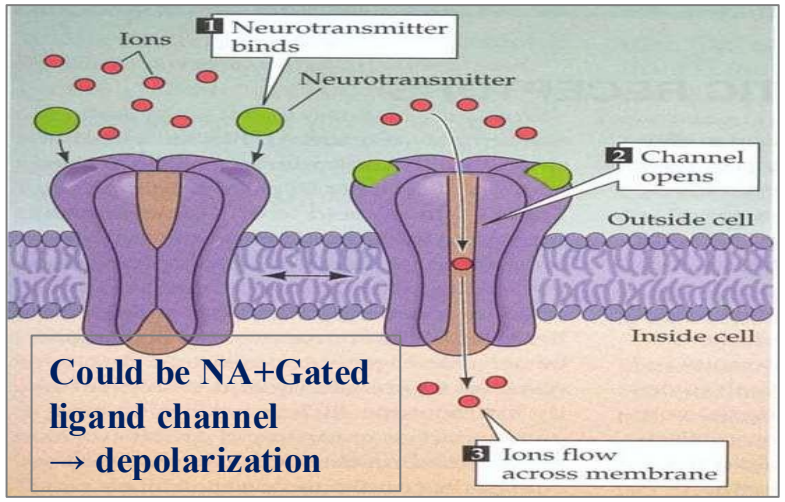
Lipid-soluble hormones act by regulating gene transcription and protein synthesis. This process of forming new proteins is slow. Usually, lipid-soluble hormones act more slowly than water-soluble hormones. This is because they work on the formation of proteins, and protein formation is a slow process, not a fast one.

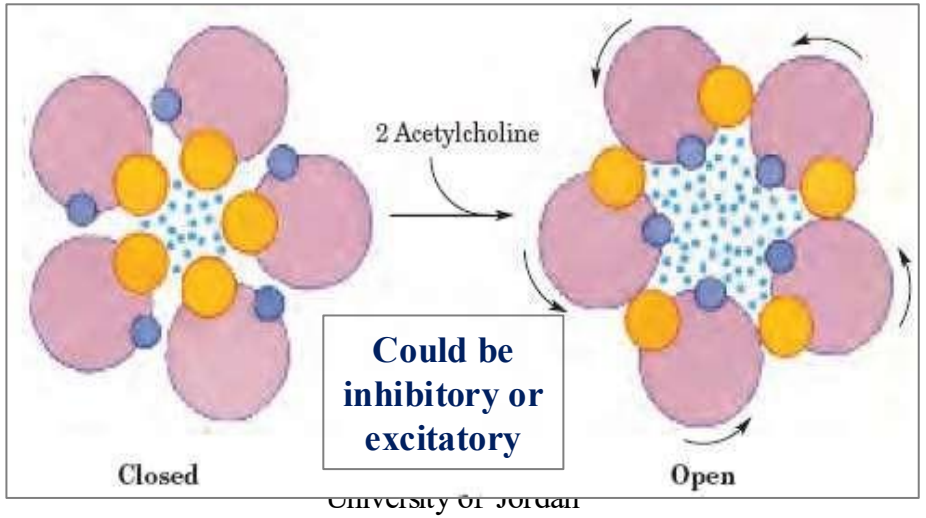
1. membrane receptors

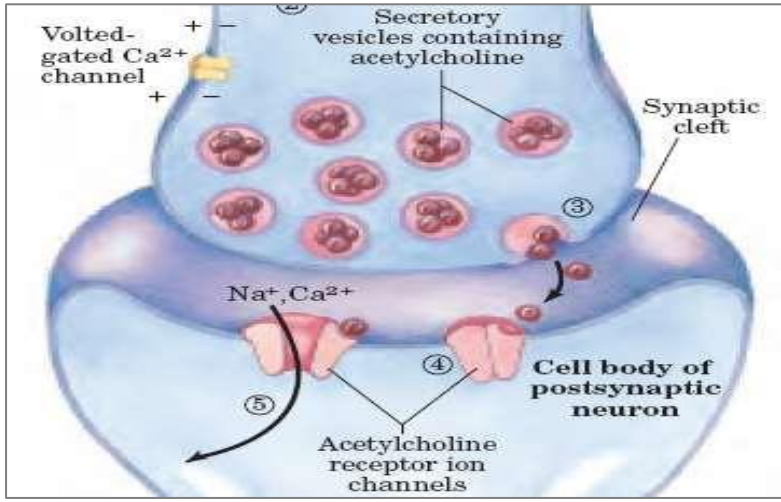
1- Ligand-gate ion channels type : if you do recall-since we obviously covered this in neurophysiology - its acetylcholine receptors, acetyl choline when it binds to its receptor it directly changes the membrane's permeability to **ions**, that's why its described as an **Ionotropic receptor** cause the receptor itself is an ion channel and opens directly when a ligand (like acetyl choline) binds

(cyclic receptor)

ligand→receptor→ion channel open or close (change in permeability)







Regarding the ligand gate ion channels

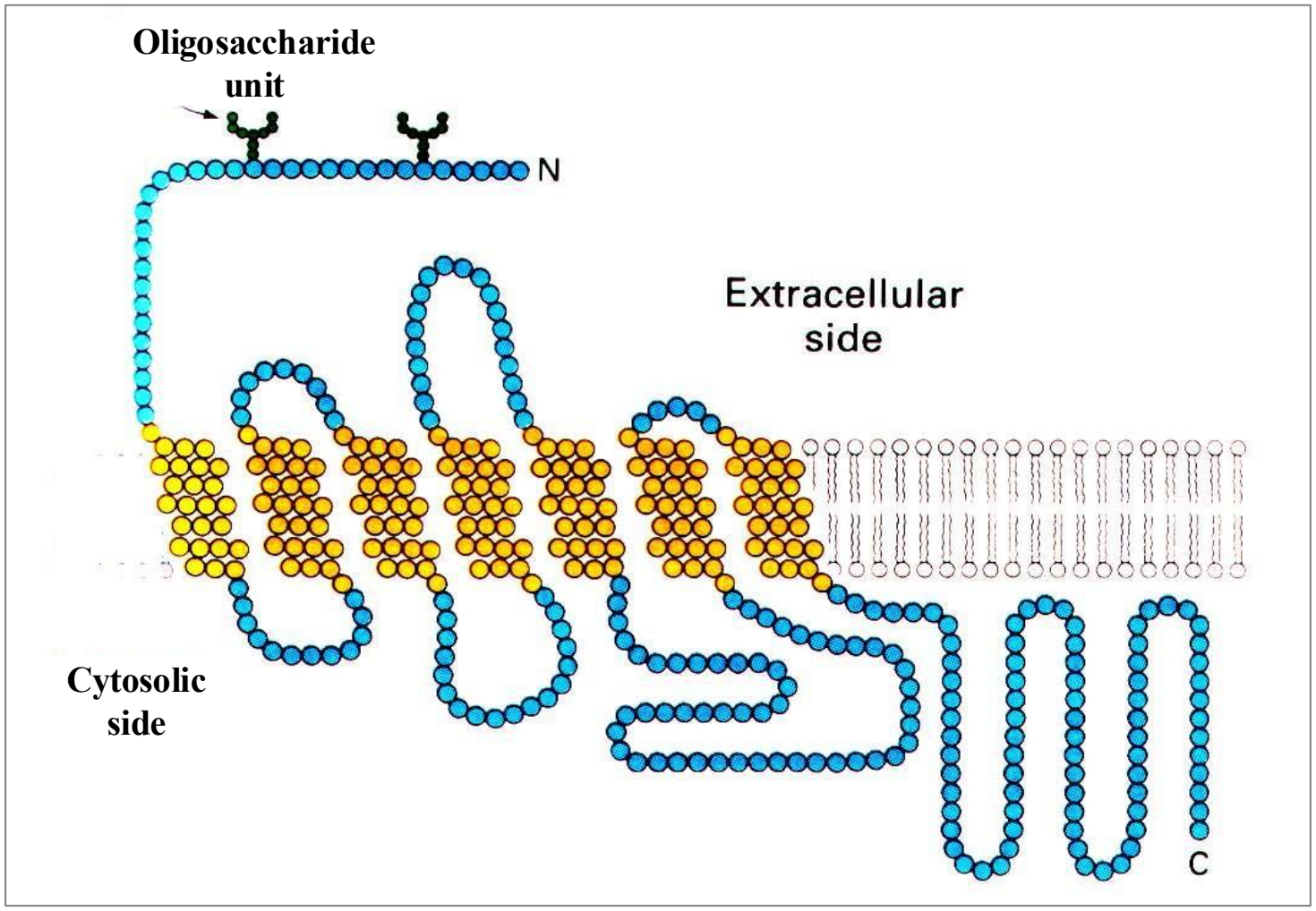
For instance , take **acetylcholine *in the heart***. It's inhibitory, meaning **it slows things down**—so you get a decrease in heart rate, slower conduction, and so on. Think about someone with a really fast heart rate. One way to calm that down is by stimulating the Vagus nerve (part of the parasympathetic nervous system), which triggers a "rest and digest" response. This stimulation releases acetylcholine directly onto the heart's natural pacemakers—the SA node and AV node—and that's what slows the heart rate. Now flip the situation. If someone has a low heart rate, we give atropine. Why? Because atropine blocks the action of acetylcholine, so it prevents that slowing effect and helps bring the heart rate back up.

HOWEVER

in the GI system , it's the opposite. Acetylcholine is **excitatory here—it increases** motility and peristalsis (Peristalsis is your gut squeezing in waves to push food through the digestive system, just like squeezing the end of a toothpaste tube to move the paste forward) That's why it can lead to things like diarrhea. So if someone has diarrhea and cramping, what do we give? Atropine again cause **here** it decreases the action of acetylcholine, which slows down those rhythmic contractions (peristalsis) in the stomach and intestines. That's why it's used to treat hypermotility and cramping. So here's the key point you need to lock in: acetylcholine dosent mean immediately "excitatory" or "Inhibtory" ,**DON'T FALL FOR THAT TRAP** . Remember from neurophysiology—the effect of a neurotransmitter depends on what? **THE RECEPTOR !** , Not the neurotransmitter itself , so the same exact idea applies to hormones too

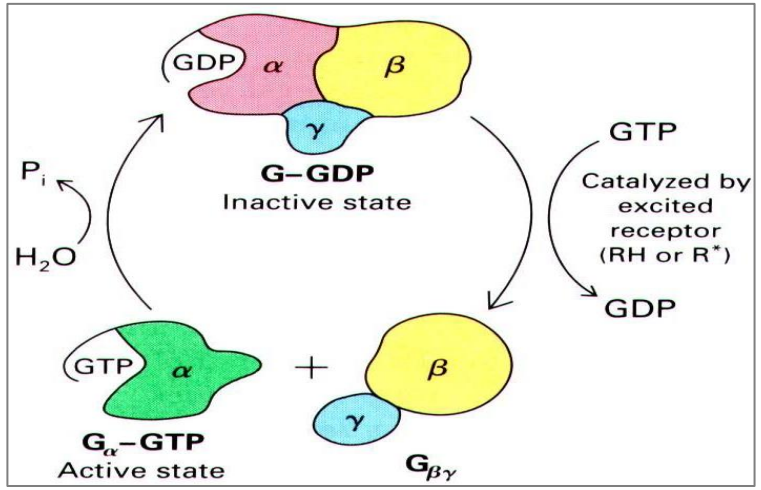
2- G Protein-Coupled Receptors

I- 7-helices transmembrane receptor (metabotropic receptor)

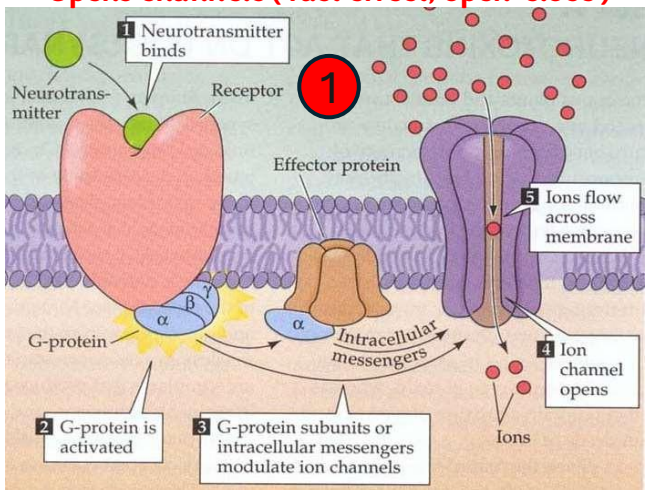


2) G protein (Guanylate binding protein)

- G protein refers to any protein which binds to GDP or GTP and act as signal transduction.
- G proteins consist of three different subunits (α, β, γ- subunit) bound to GDP when exchanged to GTP activate α-subunit (to make it smoother, **G protein** consists of alpha, beta and gamma subunits which are in **inactive** state when bound to **GDP**)
- α-subunit carries GTPase activity, binding and hydrolysis of GTP.

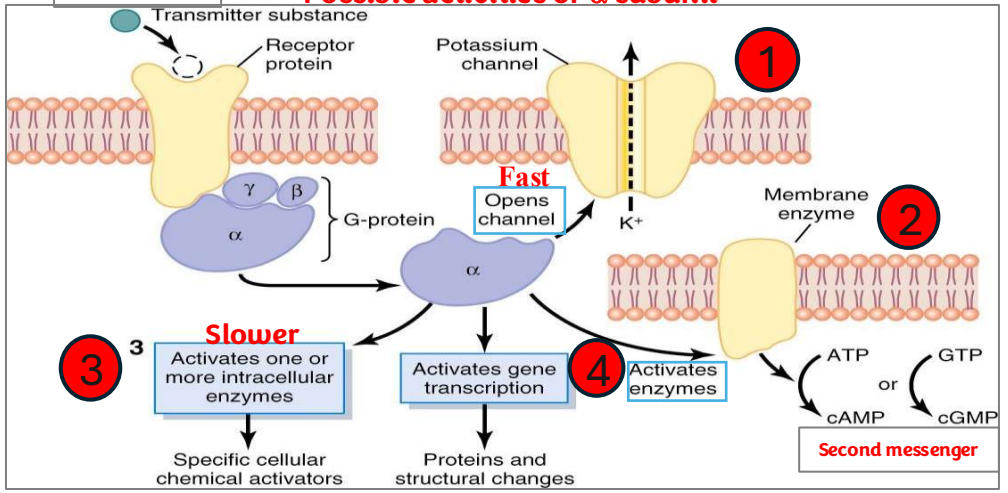


Opens channels (fast effect, open-close)

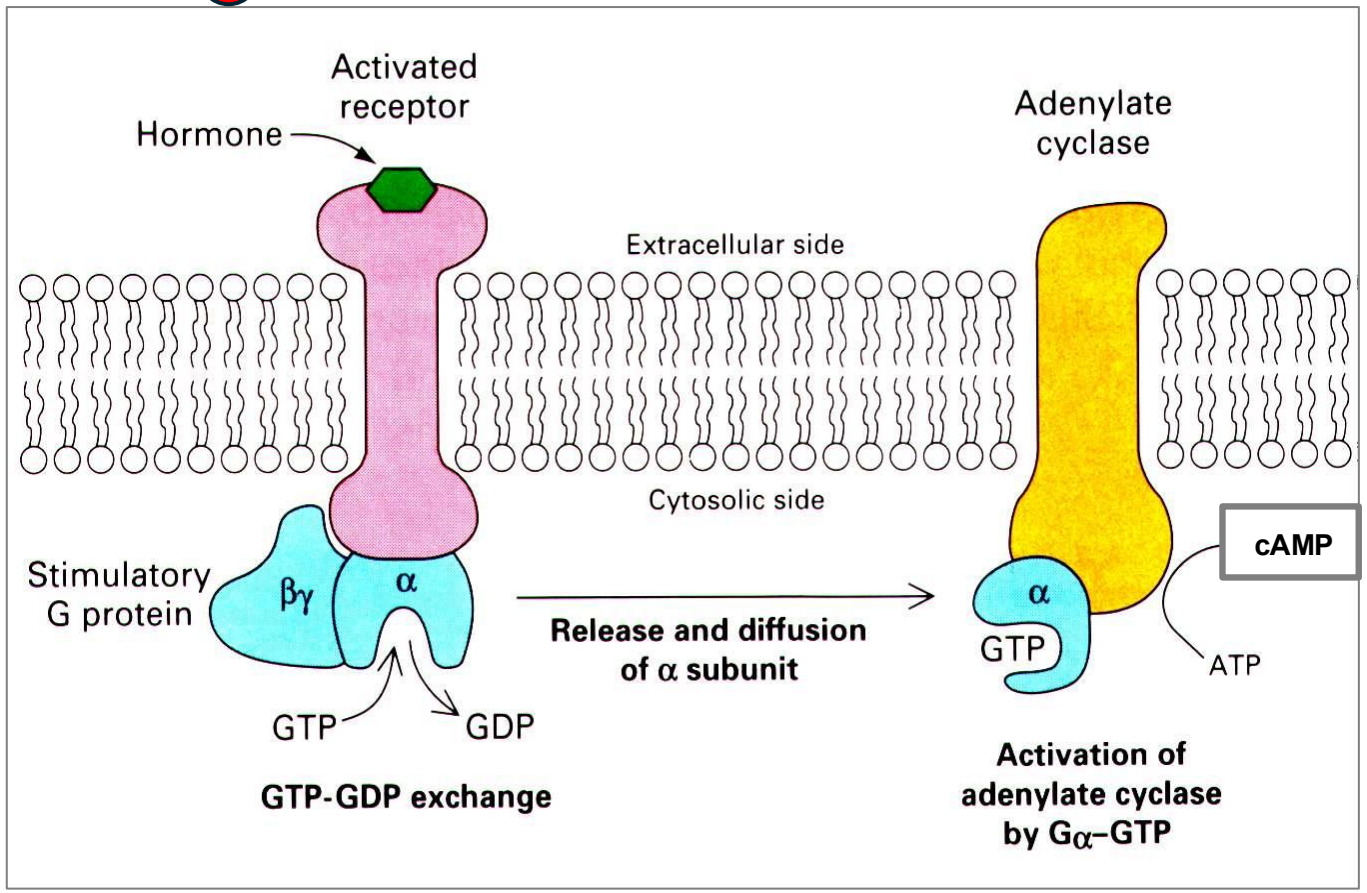


Firs messenger

Possible activities of α subunit

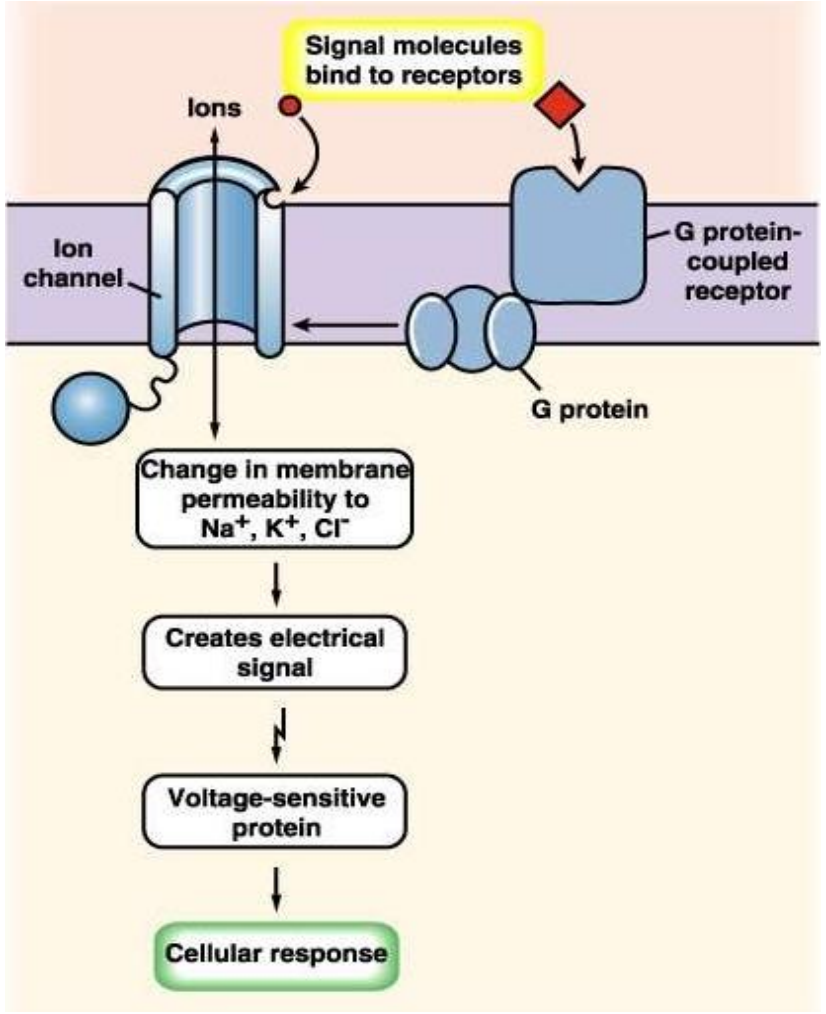


2 Enzymatic activity (activation of adenylate cyclase)



- the subunit could be excitatory or inhibitory
- cAMP is the **second messenger** here
  - It Activates **P**rotein **K**inase **A** (cAMP dependent protein kinase)
  - **PKA** phosphorylates proteins as it's name indicates Phosphorylation that may cause activation or inhibition (change in activity)

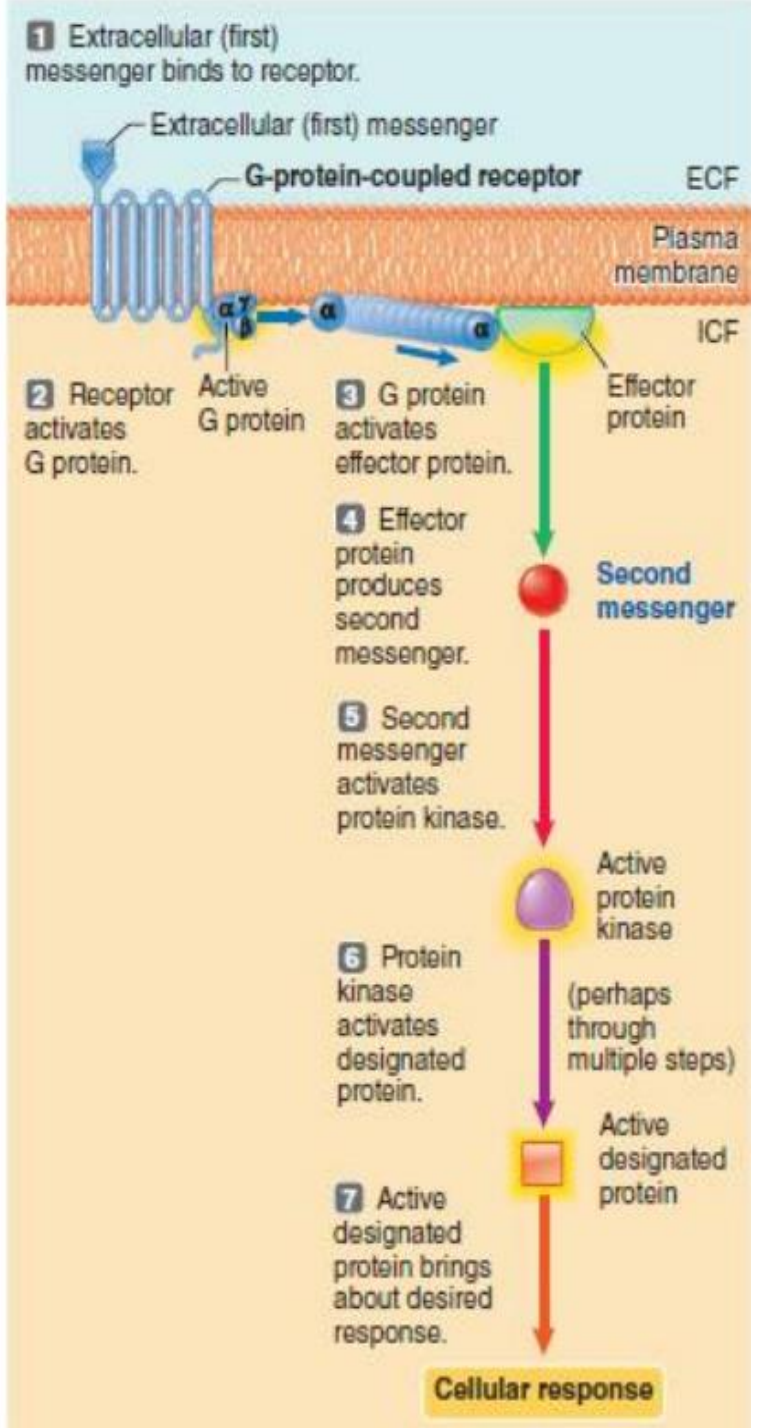
1 Opens channels (change electrical potential)



G Protein–Linked Hormone Receptors

- Binding of the first messenger to the receptor activates the **G protein**,
- On activation, a portion of the G protein shuttles along the membrane to alter the activity of a nearby membrane protein called the **effector protein**.
- Once altered, the effector protein leads to an increased concentration of an intracellular messenger, known as the **second messenger**. **Like cAMP**
- The second messenger relays the orders through a cascade of chemical reactions inside the cell that cause a change in the shape and function of designated proteins.

Amplification



To make the past 3 slides about G protein pathway easier for you since it MIGHT feel overwhelming:

Think of it like a switch getting flipped, at first, the **alpha (α) subunit** is inactive because **it's holding GDP**, then a hormone binds to the receptor, and the receptor basically goes: **"switch on."** so what happens? GDP leaves, GTP comes in and replaces it. That swap is what **activates the** α-subunit. Now that it's active, the α-subunit detaches from the receptor and moves to affect something nearby. That "something" could be a channel (it might open or close it), or an enzyme (it might activate it or shut it down). One key example is **adenylate cyclase**. When the α-subunit activates it, it **converts ATP into cAMP**. cAMP acts as a **second messenger** and then activates protein kinase A —called A because there are also B protein kinase and C protein kinase

This is where things go CRAZY with amplification as

-One hormone → activates **many α-subunits**,
-Each **α-subunit** → activates **an adenylate cyclase**
-Each **adenylate cyclase** → makes **lots of cAMP**
-Each **cAMP** → activates **many protein kinases**
-Each **kinase** → **phosphorylates many proteins**

So one small signal turns into a big effect. And last thing—phosphorylation doesn't always mean activation. Sometimes it turns proteins on, sometimes it turns them off meaning that sometimes it inhibits an enzyme and sometimes it activates it

G Protein–Linked Hormone Receptors

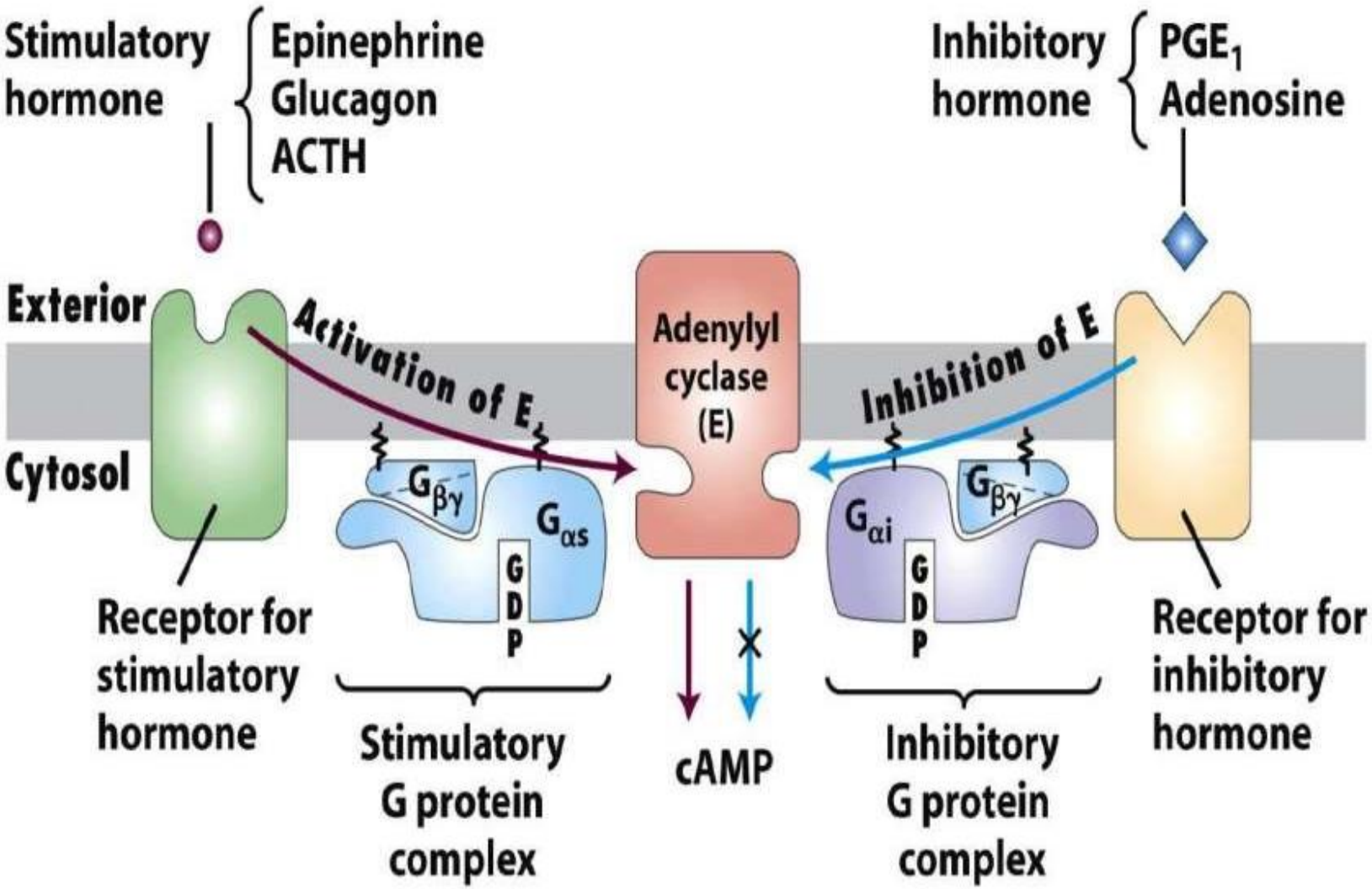


Figure 15-21

G Protein–Linked Hormone Receptors

- **Different** isoforms of $\mathbf{G_{\alpha}}$ have different signal roles. E.g.:
  - The **stimulatory** $\mathbf{G_{s\alpha}}$, when it binds GTP, **activates** Adenylate cyclase.
  - An **inhibitory** $\mathbf{G_{i\alpha}}$, when it binds GTP, **inhibits** Adenylate cyclase.

Thus, depending on the coupling of a hormone receptor to an inhibitory or stimulatory G protein, a hormone can either increase or decrease the activity of intracellular enzymes.

- The complex of $\mathbf{G_{\gamma\beta}}$ that is released when G_{α} binds GTP is itself an effector that binds to and **activates or inhibits** several other proteins.

  E.g., $\mathbf{G_{\gamma\beta}}$ **inhibits** one of several isoforms of **Adenylate Cyclase**, contributing to rapid signal turnoff in cells that express that enzyme.

G Protein–Linked Hormone Receptors

Turn off of the signal: Like in acetylcholine, relating to seizures

1. **Gα** hydrolyzes GTP to GDP + P_i. (**GTPase**).

   The presence of **GDP** on G_α causes it to rebind to the inhibitory ßγ complex.

   Adenylate Cyclase is no longer activated.

2. **Phosphodiesterases** catalyze hydrolysis of **cAMP → AMP**.

Regarding G protein pathway so that you don't get mixed up

Think of cAMP as a signal that's meant to be temporary, not something that hangs around, Its job is to act as a **second messenger—it takes the signal from the receptor and passes it inside the cell by activating protein kinase A (PKA)** so as long as cAMP is there, PKA keeps working, and the whole response keeps going but here's the problem: **if cAMP stays for too long, the signal doesn't stop, It just keeps running. that's why the cell has to shut it down quickly**. It's similar to **acetylcholine in the brain**—if acetylcholine keeps stimulating without stopping, you get continuous activity, which can lead to things like seizures. **Same idea here,** signals must be tightly controlled and turned off at the right time so cAMP doesn't **"want"** to stay as cAMP. It needs to be broken down into something **inactive so the signal stops.** The enzyme responsible for that is **cAMP-dependent phosphodiesterase**. Since cAMP is a cyclic molecule (a "diester"), this enzyme breaks that ring **and converts it into AMP, which is inactive**. That way, the signal is terminated. And just to be clear , the phosphodiesterase that breaks down **cAMP** to **AMP** is **different** from the one that breaks down **cGMP → GMP** so **DON'T MIX UP**

continuing with the signal turn-off from the slide before :

First, the **α-subunit (Gα)** itself shuts down. It hydrolyzes **GTP to GDP + Pi** (this is its GTPase activity). **By the way here, Pi just means inorganic phosphate—you can think of it as a small phosphate piece that gets released when GTP is broken down. When GDP is back on the Gα subunit, it becomes inactive again and rebinds to the βγ complex (Gβγ).**

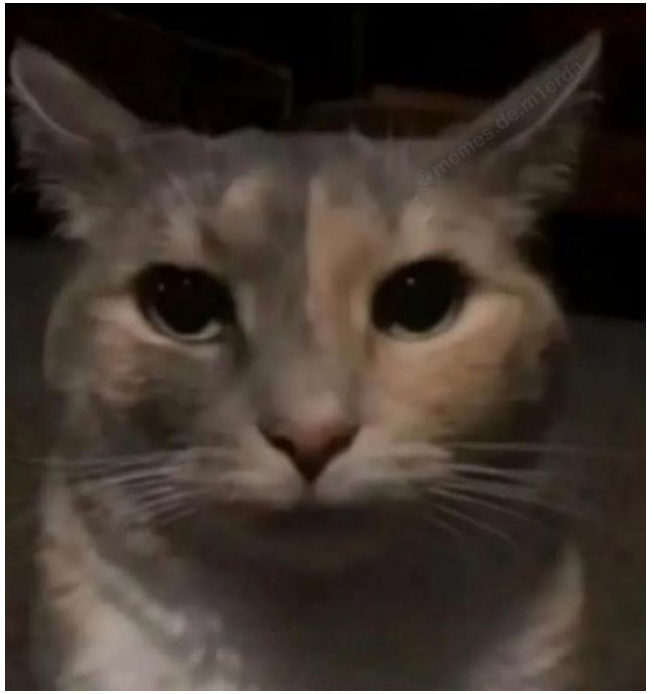
Just a head up : There are **different types** of the **Gα subunit: Gαs (Gs alpha)** ⟶ it stimulates **(activates) adenylate cyclase**, **Gαi (Gi alpha)** ⟶**it inhibits adenylate cyclase** , so depending on **which type** is present, the signal can either increase or decrease. Also, the **Gβγ (beta-gamma complex)** is not just sitting there—it can also act on other proteins and activate or inhibit them. As a result of Gα becoming **inactive again**, adenylate cyclase is no longer activated.

This concept is actually used in drugs. Some drugs are designed to **inhibit phosphodiesterase**, meaning they stop the breakdown of the second messenger, **so the signal lasts longer**. A very well-known example is **Viagra**, which inhibits the cGMP-dependent phosphodiesterase—not the cAMP one.

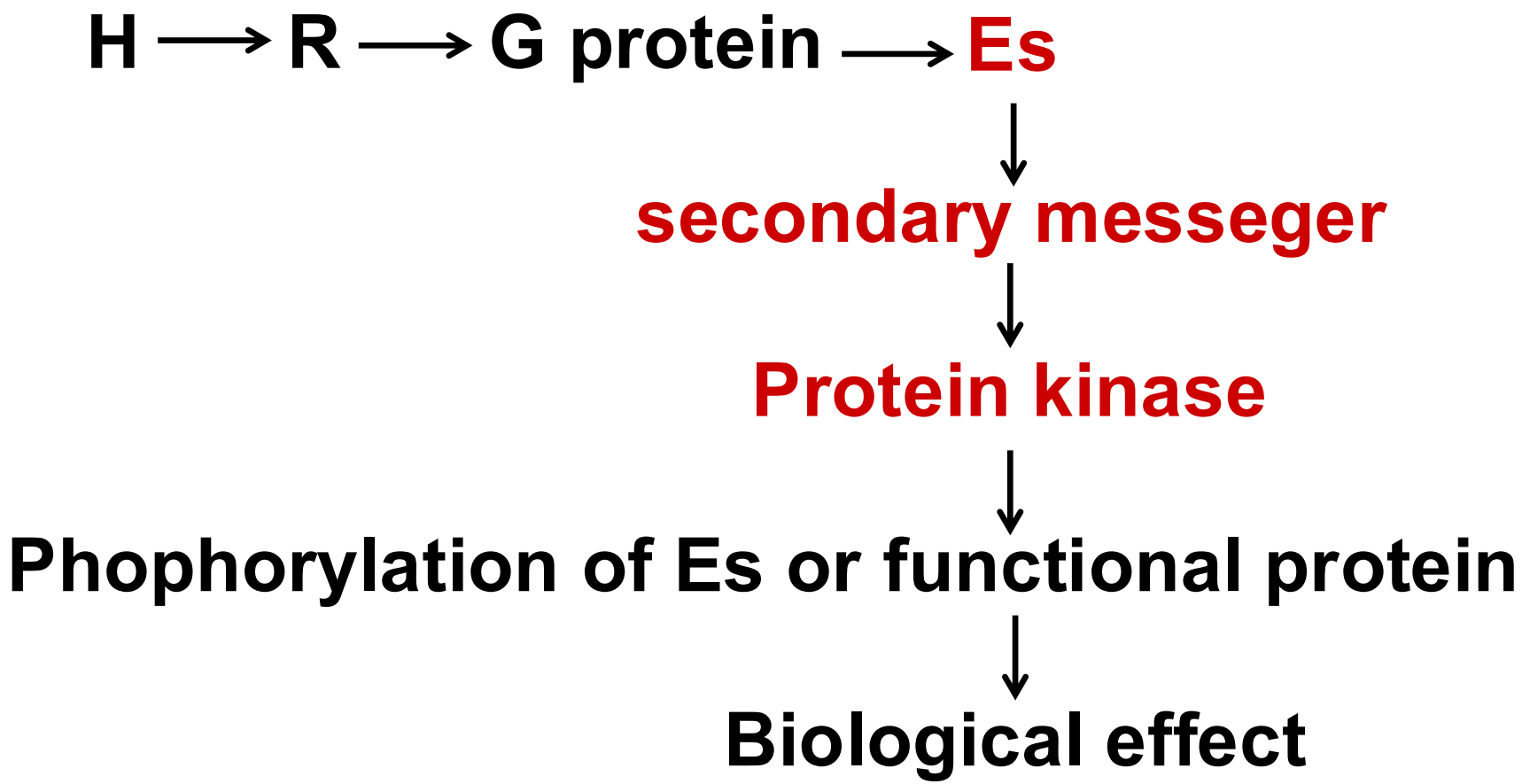
IMPORTANT : Some might get mixed up with the last 3 slides of G protein pathway thinking it's a separate step that happens after everything is finished, like: first the hormone acts, then amplification happens, then later the cell shuts it off. But that's not really what's happening. Although the professor didn't clarify this point clearly BUT :

In reality, the **"turn-off"** mechanisms **are happening at the same time as the signal**. While the pathway is being activated and amplified, **the cell is already working in the background to stop it, so no its not a separate thing that happens after the pathway is done—it's actually part of the same G-protein pathway, just the "turning off" phase of it**. . It's more like a system that has the gas and the brakes pressed together, but in a controlled way.

That's why the signal doesn't go on forever, think of the whole thing as **one continuous sequence:** First, **the hormone binds** then **G protein gets activated** then **α-subunit activates adenylate cyclase → cAMP is produced** then **amplification happens**. so the system already has built-in mechanisms to stop the signal. It doesn't wait until everything is finished— **these "off" processes** are happening **in parallel while the signal is going on** . So instead of thinking: start then amplify then stop (in separate steps)
Think: start + amplify + stop all overlapping together within the same pathway



- Pathway of G protein linked receptor



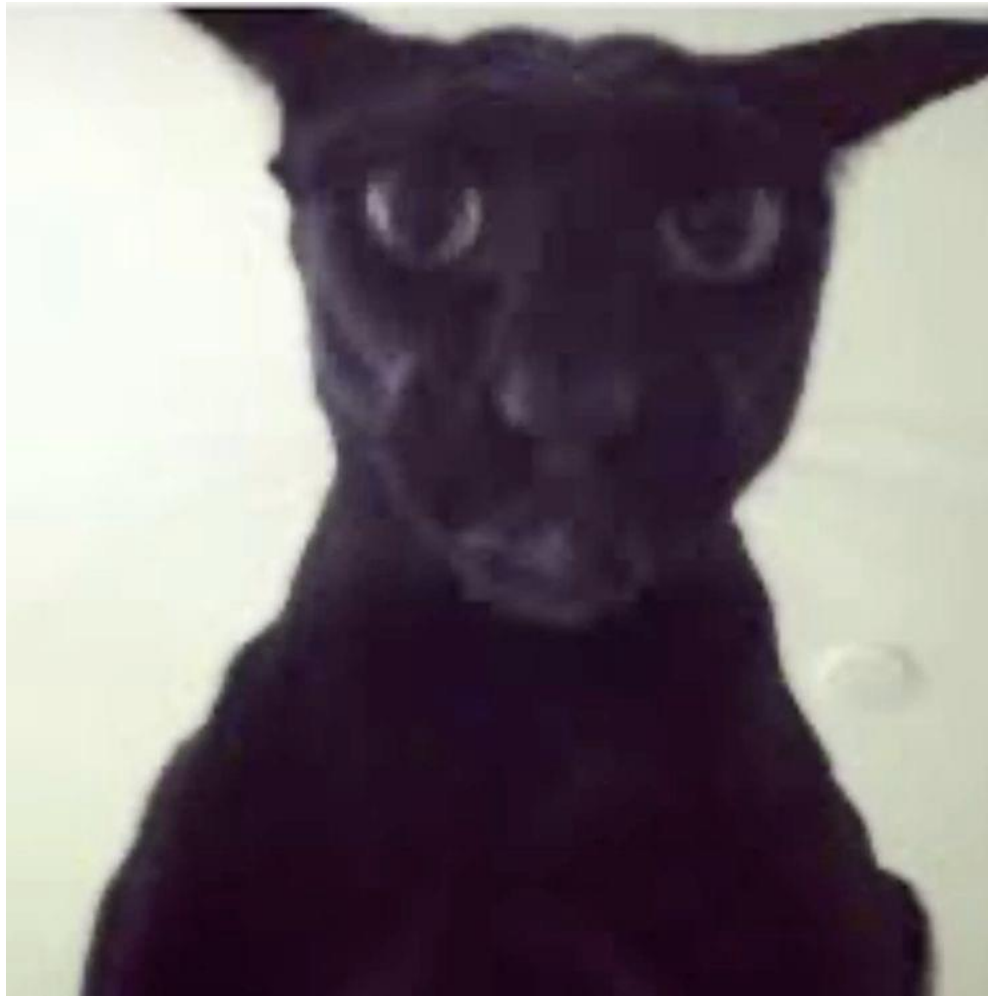
Receptor Types

- Channel-linked receptors
  - Ionotropic
- Enzyme-linked receptors
  - Protein kinases → phosphorylation
  - **Neuro**trophins
- G-protein-coupled receptors
  - Metabotropic
- Intracellular receptors (lipid soluble)
  - Activation by cell-permeant signals ~

Properties of binding of H and R

- high specificity
- high affinity
- Saturation (Vmax)
- reversible binding
- special function model

Larry wants to test you



For any feedback, scan the code or click on it

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1			
V1 → V2			

Additional Resources:

رسالة من الفريق العلمي:

لا بأس بأن تجد صعوبة في تلقي معلومة معينة خاصةً إذا كانت جديدة، تذكّر دائمًا أن " العلم بالتعلّم "، فمهما استغرقت من الوقت لدراسة وتعلّم شيءٍ ما، فلتعلم أنك سوف تتقنه بإذن الله وسوف تؤجر على جهدك، ولتسعَ دائمًا لكسب العلم لا العلامة يا طبيبَ المستقبل .

Reference Used:
(numbered in order as cited in the text)

1. Dr’s slide & lecture