The Endocrine System

BIOCHEMISTRY

☑ Sheet ☐ Slide ☐ Handout

Number:	3
Subject:	Hormone Receptors
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Revision

In the previous lectures, we talked about hormones in general and the interaction between the nervous and the endocrine system.

- What's the problem with the endocrine system? Hormones are produced far from their target, so they have to be effective and to saturate the receptors. How can this problem be overcome?
    1. Enhancing the specificity of the receptors for the hormones.
    2. Increasing the affinity between the hormone and the receptor.

We talked about factors affecting the response, specificity and affinity expressed as $\mathbf{K_d}$ which is the dissociation constant.

We also talked about the structure of hormone receptors and that they are composed of two domains, the recognition domain and the coupling domain.

- Why do we need amplification in the endocrine system for hormones? Because we won't achieve our goal otherwise. Our cells don't have enough receptors.
  Plus, hormones are produced in very small amounts; we can't produce them in large amounts because we would need more receptors, the membrane of a cell would be mostly made of receptors, not practical and unachievable

We talked about the classification of hormones according to the mechanism of action and according to the chemical structure and how they are different from each other, just be familiar with them, you won't be asked about a specific structure.

And lastly we talked about the target cell interactive effects; permissive effects, integrative effects, synergistic effects and antagonism.

Transduction

Transduction: the *conversion of one form of a signal to another so as cells can produce many kinds of responses in different ways*.
Transduction is how amplification goes on within cells. *Amplification is a must*.

Hormones bind to transmembrane **receptors** (receptors that span the membrane projecting inside and outside; *have intracellular and extracellular regions*).

Transmembrane receptors are *intrinsic* proteins (proteins that can't be extracted out of the membrane experimentally).

- Why do we have transmembrane receptors?
  To bind hydrophilic hormones (polypeptides, proteins, glycoproteins, catecholamines, amino acid derivatives).
- Are the receptors enough to transmit the signal? They're not. They are *few in number and their movement is restricted*, there has to be a second messenger.
- What are the properties of these second messengers? They have to be hydrophilic (water soluble) to be able to *diffuse to other cellular compartments*, to reach their target
- Amplification occurs within the cell. How is amplification achieved in the end? How can we biochemically achieve big results within a small amount of time?
  Enzymes can produce big amounts within a short period of time.

Second messenger systems either involve enzymes or ***channels***, channels open up to move large concentrations all at once from one place to another, so you end up with a change in the whole concentration within a short period of time.

The hydrophilic hormones that bind to receptors on the cell membrane have second messengers. One of the most important second messengers is cAMP.

- cAMP is the second messenger for approximately 30 hormones, so how do we have **different outcomes**? What makes cells different?
  The transcription profiles of cells is what makes them different. You won't find the same proteins in all cells, each cell expresses a specific receptor which binds to a specific hormone.

Therefore, even though cAMP is the common second messenger for 30 hormones, the outcome will differ depending on the type of cell that is stimulated.

- Why do we have **30 hormones** that use the same second messenger? To control the functions in the body (i.e. for regulation).

We could only have one hormone which binds to only one type of receptor and the result would still be cAMP, and it would still have different functions in different types of cells, but this isn't practical.

On the other hand, when there is more than one type of hormone and more than one type of receptor (which is what we actually have), different procedures could be operated within the body with better regulation.

- What if we had only one receptor?
  The 30 different hormones have 30 different structures, so accordingly, if there is only one receptor that will bind those 30 hormones, the degree of binding would be different → different Kd → some hormones would function more than they should and some would function less, producing odd amounts of cAMP.
  This is why you need different hormones with different receptors.

Types of 2nd messengers:

1. Small molecules (cAMP, cGMP, Ca^{+2}).
2. Phosphorylation through kinases.

After a signal is being transmitted within cells of the body, it needs to be terminated, but why?

1. Regulation of cell function
   The hormone has to come off and it has to bind again whenever needed. I need it to be on or off *to keep the cell responsive to other signals.*
2. To prevent occurrence of cancers
   For example, growth hormones would keep cells proliferating, thus forming a neoplasm.

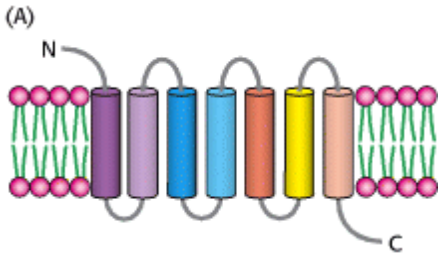
How is the signal terminated?

1. The second messenger within the cell undergoes *degradation by enzymes.*
2. The amount of the hormone decreases, which leads to less binding of the hormone molecules to the receptor. What about the ones that are already bound? They get released due to the fact that their binding is *reversible (non-covalent)* and reversible binding is always *controlled by concentration*. An increase in the concentration will result in stronger binding and if you *decrease it then releasing the hormone from the receptor will be higher*.
3. *Dephosphorylation by hydrolysis (via phosphatases)*.

The type of receptor can have an effect. There are two types of receptors: the first is called **7-transmembrane helix receptor (7TM)**, and the second is **receptor tyrosine kinase.**

7TM is very common for a lot of hormones; that's why it's going to be explained.

As the name implies, it's a hormone receptor which has 7 α helices, a part of it is inside the membrane and a part is outside.



α-helices are hydrophilic in their nature, so when the hydrophobic content is high, it disrupts the α-helical structure, one of the things that give the helix its shape is the high content of hydrophobic amino acids.

Therefore, how can you insert something that's hydrophilic into the membrane? **Hydrophilic** structures can make hydrogen bonds. What happens is that the amino acids within the helix make extensive hydrogen bonds with each other; this inhibits any amino acid from making hydrogen bonds with any other structure.

The structure that I have now within the α helix is very rigid and is hydrophobic, it can't bind with anything else, although it is hydrophilic in nature, but *the resulting structure is hydrophobic due to the extensive hydrogen bonding.*

- On the cytoplasmic side, the protein has many serine and threonine residues, why? Because they can be phosphorylated since they have oxygen.
- Why do I need to phosphorylate them? To change the conformation of the receptor, accordingly it changes the activity of the receptor.

A lot of hormones are working on 7TM receptors:

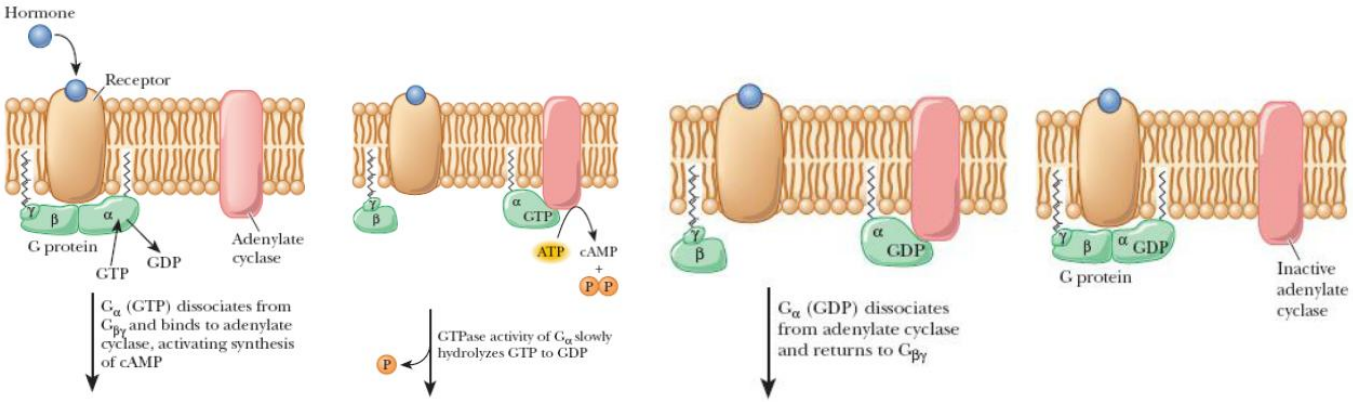
- All 7TM receptors transmit their message via a **2nd messenger**.
- All 7TM receptors are coupled to **G-proteins,** which means they can be called G-protein coupled receptors.
  So when you hear "G-protein coupled receptors" or "GPCR", you should immediately think of receptors which transmit their message through G-proteins.

Biological functions mediated by 7TM:

- ✓ Smell, taste and vision
- ✓ Neurotransmission
- ✓ Hormone secretion
- ✓ Chemotaxis
- ✓ Exocytosis
- ✓ Cell growth and development
- ✓ Viral infection

G-proteins

G-proteins are trimeric proteins, they have 3 subunits, α, β and γ. α can leave the complex, while β and γ are connected to each other. If you take a look at their structure, β and γ are connected as one unit, α is connected to them but it can dissociate. α and γ are connected to the membrane covalently through the attachment of fatty acids, to be able to hold the G-protein close to the membrane. The G-protein is a bit far from the receptor, but once a hormone binds to it, it creates a conformational change within it attracting the G-protein, once the G-protein comes in close proximity to the receptor it gets activated, which is the second messenger system starting point.



- How does the G-protein get activated?
  1. The inactive form bound to GDP, and it becomes active through replacing GDP with GTP.
  2. Once GTP is bound the G-protein gets activated, the α-subunit will dissociate from the complex.
  3. When it dissociates it performs its action. Its most common action is to activate the enzyme adenylate cyclase, which converts ATP to cAMP (this is how the second messenger is produced).
- Are there any other routes that the alpha subunit could go through?
  Yes, it could go to phospholipase C, and another way of activation is to open or close channels.
- Does the alpha subunit always activate things, or could it inhibit them?
  Till now, there are around 20 types of normal G-proteins. Whenever scientists discover one, they look at the α subunit to see if it has the same amino acid sequence, if it was a little different then they give it a new name.

Examples on the Gα subunits:

- G_s (stimulatory) → stimulatory; *increases the action of adenylate cyclase.*
- G_{olf} (olfactory) → *also increases the action of adenylate cyclase*.
- ***Transducin*** (retina) → *increases the action of cGMP phosphodiesterase.*
- G_i (inhibitory) → *decreases the action of adenylate cyclase.*
- G_o (open) → *opens calcium channels.*
- G_q → *activates phospholipase C.*

Although a lot of forms of Gα subunits exist, they all either activate or inhibit. Some of them are inhibitory, but most of them are stimulatory.

- After the alpha subunit dissociates and activates the adenylate cyclase, we need to deactivate the alpha subunit and stop the signal, how does that happen?
  The alpha subunit is active and binding, for example, adenylate cyclase. Adenylate cyclase is producing more and more cAMP. How can this process be shut down? The α subunit itself is an enzyme, it can break the GTP which is bound to it, it takes out one phosphate group and turns GTP into GDP, which deactivates the alpha subunit, now it can bind the βγ complex again stopping the signal.
- The α-subunit is either stimulatory or inhibitory. Is there anything other than the nature of the α-subunit or the G-protein that determines how the signal will be processed within the cell to decide whether the signal is stimulatory or inhibitory?
  Yes, the receptors are different from each other. Some are stimulatory in their nature so they only bind to a stimulatory G-protein, like β1-adrenergic receptors. On the other hand, others are inhibitory; they only bind to inhibitory G-proteins, like α2-receptors.

In the end, what decides whether the signal is stimulatory or inhibitory is the nature of the α-subunit and the type of receptor that binds the hormone.