Chemical Coordination and Integration - Part 3

Content Outline

- Introduction
- Transmembrane Receptors
  - G-protein coupled receptors
    - Mechanism of Action
  - Enzyme-linked receptors or kinase receptors
    - Mechanism of Action
- Intracellular Receptor
    - Mechanism of Action
- Summary

Introduction

Hormones are the endocrine mediators that are produced by specialized cells/endocrine glands and act on specific target cells. Hormones show their effects on target tissues by binding to specific proteins present on the surface of target cells. These proteins are known as **hormone receptors.** Every hormone has a specific receptor that is present on the target cell. The hormones may be present on the cell surface and are known as **membrane-bound receptors** or they may be present in cytoplasm and are known as **intracellular/soluble receptors** and are mostly **nuclear receptors** i.e. present in nucleus.

When a hormone binds to its receptor it forms a hormone-receptor complex. This binding stimulates certain biochemical changes in the target tissue. The interaction between hormone and its receptor shows some characteristic features like the interaction is highly specific, reversible, has high affinity and occurs only in the target or receptive tissue. Based on their structure and chemical nature, hormones can be divided into following groups:

1. **Peptide hormones:** For example – Oxytocin, vasopressin, GnRH, GHRH, TRH, Somatostatin etc.
2. **Polypeptide/Protein hormones:** For example –insulin, glucagon, gastrin, secretin, CCK, calcitonin, prolactin, Growth Hormone etc.
3. **Steroid hormones:** For example – Estrogen, progesterone, testosterone, aldosterone, cortisol etc.

4. **Iodothyronines:** For example - Triiodothyronine (T3) and thyroxine (T4)
5. **Amino acid-derivatives:** For example – Dopamine, melatonin, epinephrine, norepinephrine.

The hormones which interact with the membrane bound receptors do not enter the cell but they bring about the biochemical changes through second messengers. **Second messengers** are small intracellular and diffusible molecules which are produced after the first messenger (hormone or other ligand) binds to the receptor. The second messengers activate the intracellular signaling pathways which result in the cell-specific response. For example, **cyclic 3',5'- adenosine monophosphate** (cAMP) is a water soluble second messenger. It is formed from ATP by the action of the enzyme **adenylyl cyclase**. It further propagates the signal by activating **protein kinase (PK)**.

Other second messengers include lipophilic second messengers derived from phosphatidylinositol (PI), for example **1,2-diacylglycerol** (DAG) and **inositol 1,4,5-triphosphate** (IP3). They propagate their signals by activating **phospholipase C (PLC)**. Calcium which is generally sequestered in mitochondria and endoplasmic reticulum (ER) also acts as a second messenger for many hormones. Calcium binds with calcium binding proteins and brings about physiological changes.

Most of the hormones, other than steroid hormones, such as the peptide and protein hormones can't enter the cell as they are hydrophilic hence their receptors are located on the plasma membrane. The hormones, such as steroid hormones and iodothyronine hormones, interact with the intracellular receptors and mostly regulate the expression of the genes by binding to specific sequences in the genome. Thus, the cascade of biochemical reactions initiated by binding of hormones with their receptors causes physiological and developmental effects.

Transmembrane Receptors

The transmembrane receptors are located on the plasma membranes. There are two major types of transmembrane receptors:

a. G-protein coupled receptors (GPCRs):

The G-protein receptors are a single chain of polypeptide which crosses the lipid bilayer seven times and form 7-transmembrane domains. The G protein is attached to the

cytoplasmic side of the receptor. The G-protein coupled receptors are also called serpentine **receptors** (Figure 1).

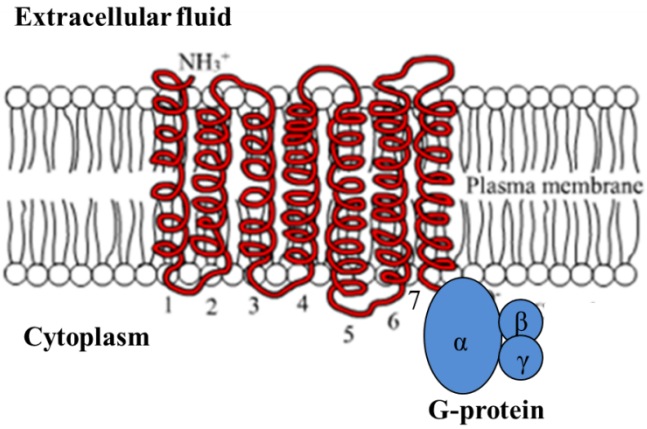

Figure 1: General structure of a G-protein coupled receptor

Source: https://en.wikipedia.org/wiki/Follicle-stimulating_hormone_receptor

i. Mechanism of Action

The **G-proteins** consist of **three subunits**: **α, β and γ**. When the cells are not stimulated, the α-subunit remains bound to **GDP** and G-protein remains **inactivated**. When the hormone binds to the GPCR, the α-subunit releases GDP and replaces it with **GTP**. Due to this binding, the G-protein is then divided into two active components i.e. the **α-subunit** and **βγ complex**. The α-subunit of G-protein is actually an enzyme known as **GTPase** (enzyme which hydrolyzes GTP to GDP and produces energy). In this form i.e. **α-GDP**, it again binds to the βγ complex and forms the inactive G-protein (Figure 2). Thus, the same receptor can be used again and again by the ligands (i.e. hormones).

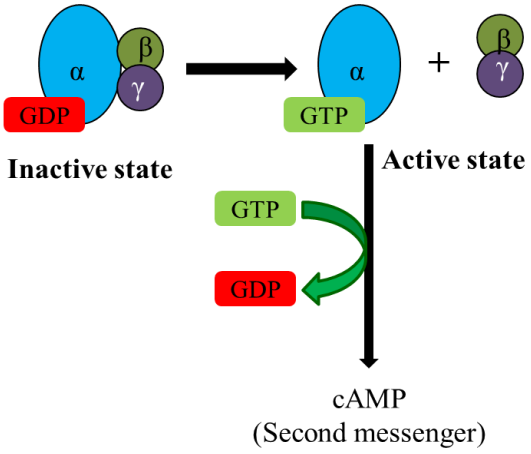

Figure 2: Activation of G-protein

Source: Author

b. Enzyme-linked receptors or kinase receptors

Enzyme linked receptors are transmembrane receptors which have only one transmembrane domain. They have an enzyme attached at the cytoplasmic side which activates further proteins. In most of the cases, the binding of hormones activates the cytoplasmic enzyme associated with the receptor. For example, the common enzymes associated with the receptors are serine/threonine kinase, tyrosine kinase and guanylyl cyclase.

i. Mechanism of Action

The binding of hormones to the receptor causes the receptor to dimerize i.e. the two molecules of the receptor come closer due to covalent binding. Dimerization causes the associated enzyme to get activated which further activates more proteins and brings about physiological changes (Figure 3).

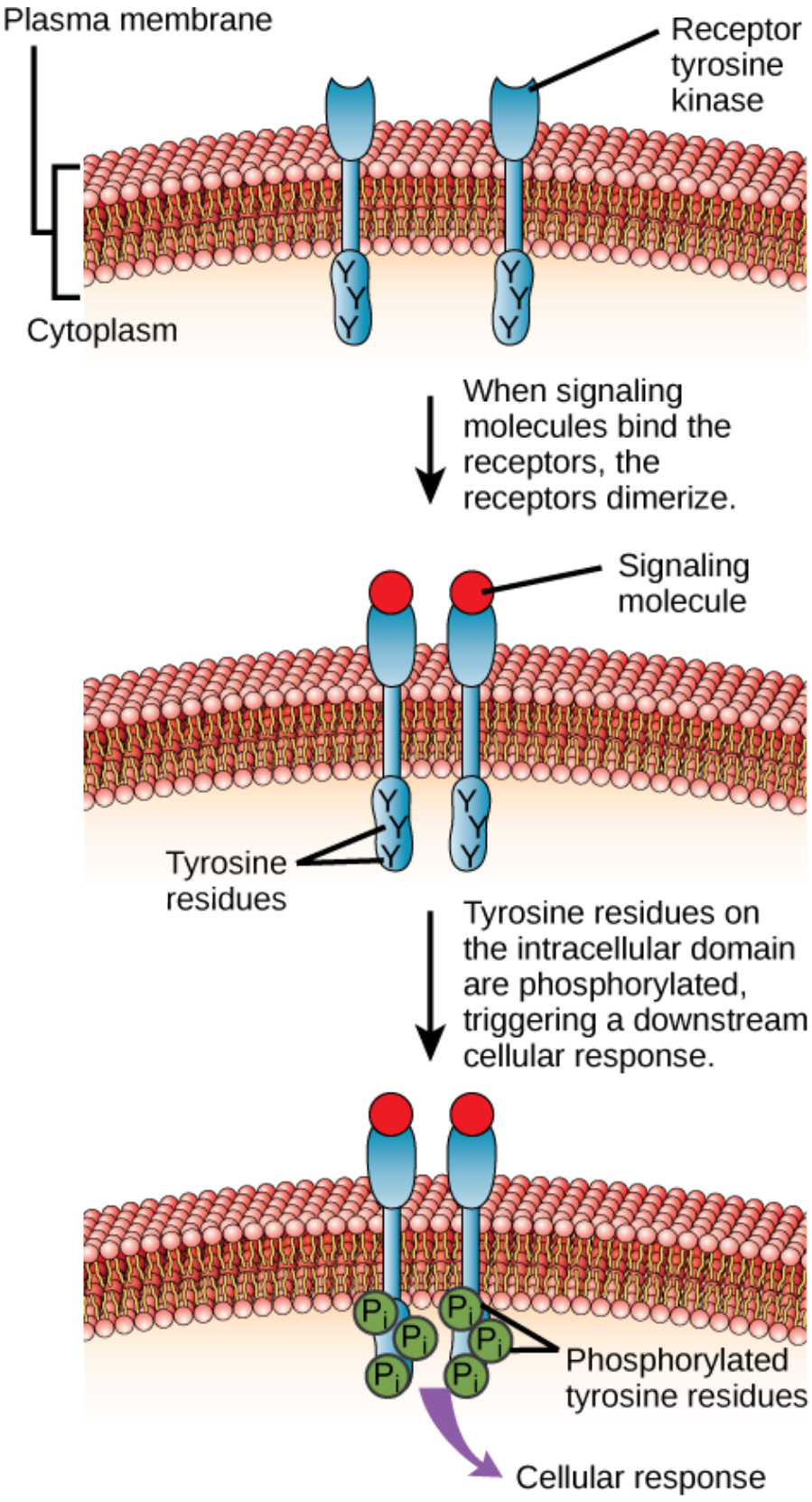

Figure 3: Mechanism of action of enzyme-linked receptor

Source: https://commons.wikimedia.org/wiki/File:Figure_09_01_07.png

Intracellular Receptors

Steroid and thyroid hormones exert their effects by binding to intracellular receptors. The hormones that bind to intracellular receptors are membrane permeable. When the hormone is not available, the receptor remains bound to heat shock protein 90 (HSP 90) which keeps the receptor in an inactivated state. The steroid hormone receptors consist of following domains (Figure 4):

a. N-terminus domain: This domain is variable and modulates transcription of the gene.
b. A central DNA-binding domain: This domain binds to the specific sequences on the DNA.
c. A C-terminus or ligand binding domain: This domain binds to the hormone.

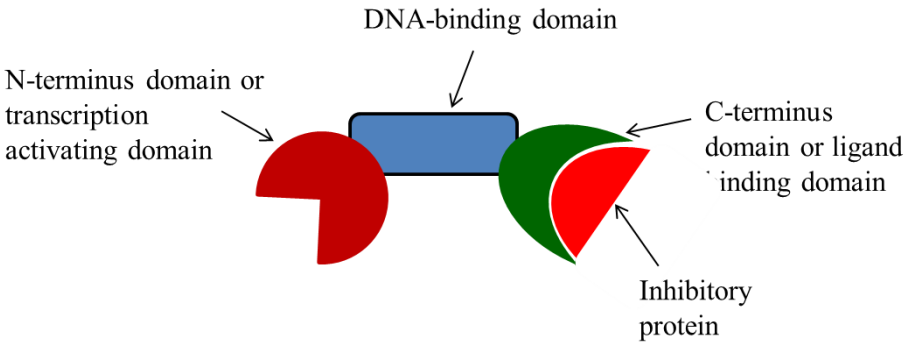

Figure 4: General structure of an intracellular receptor

Source: Author

i. Mechanism of Action

When the hormone binds to the receptor, the heat shock protein is released and the receptor dimerizes and translocates to the nucleus. Inside the nucleus, steroid receptor acts as a transcription factor i.e. it binds to the specific regions of the DNA and stimulates the transcription of the gene and brings about the cellular response (Figure 5).

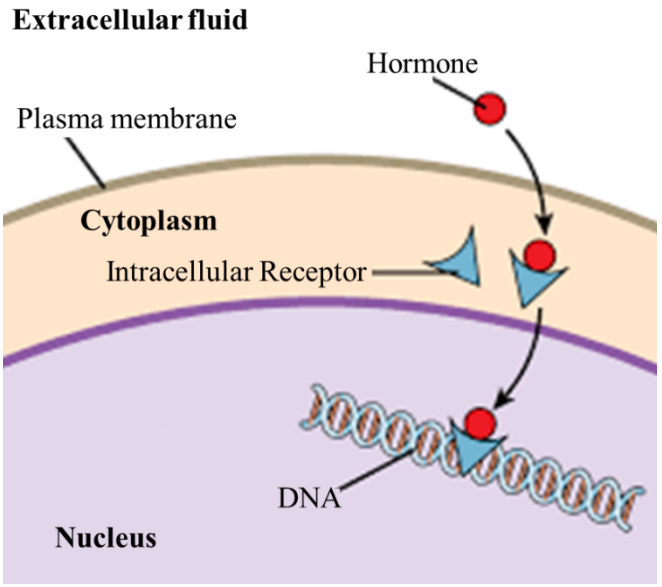

Figure 5: Mechanism of Action of intracellular receptor

Source: https://commons.wikimedia.org/wiki/File:Figure_09_01_03.jpg

Summary

Hormones are the endocrine mediators that are produced by specialized cells/endocrine glands and act on specific target cells. Hormones show their effects on target tissues by binding to specific proteins present on the surface of target cells. These proteins are known as hormone receptors. The hormones may be present on the cell surface and are known as membrane-bound receptors or they may be present in cytoplasm and are known as intracellular/soluble receptors and are mostly nuclear receptors i.e. present in nucleus. The hormones which interact with the membrane bound receptors do not enter the cell but they bring about the biochemical changes through second messengers. Second messengers are small intracellular and diffusible molecules which are produced after the first messenger (hormone or other ligand) binds to the receptor. The second messengers activate the intracellular signaling pathways which result in the cell-specific response.For example, cAMP, IP_3, Ca^{2+} etc. The receptors can be divided into two groups: transmembrane receptors and intracellular receptors. The transmembrane receptors are located on the plasma membranes. There are two major types of transmembrane receptors: G-protein coupled receptor and enzyme-linked receptor. The G-protein receptors are a single chain of polypeptide which crosses the lipid bilayer seven times and form 7-transmembrane domains. The G protein is attached to the cytoplasmic side of the receptor. The G-protein coupled

receptors are also called serpentine receptors. The G-protein propagates the signal through cAMP as the second messenger. Enzyme linked receptors are transmembrane receptors which have only one transmembrane domain. They have an enzyme attached at the cytoplasmic side which activates further proteins and brings about physiological changes. The enzymes associated with these receptors include tyrosine kinases, serine/threonine kinases etc. The intracellular receptors are found in the cytoplasm or in the nucleus. They remain bound to inhibitory proteins such as HSP90. When a hormone binds the receptor, it dimerizes and enters the nucleus. Within the nucleus it binds to a specific region on the DNA and stimulates the transcription of the gene. The transcription of genes and further events carry out the physiological changes associated with the hormone.