

UNIT-II

Mechanisms of hormone action and target cell interactions

Chemical Bioregulation in Physiological functions

Course No. – VPY- 609

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Introduction

- A hormone is a secreted chemical messenger that enables communication between cells and tissues throughout the body.

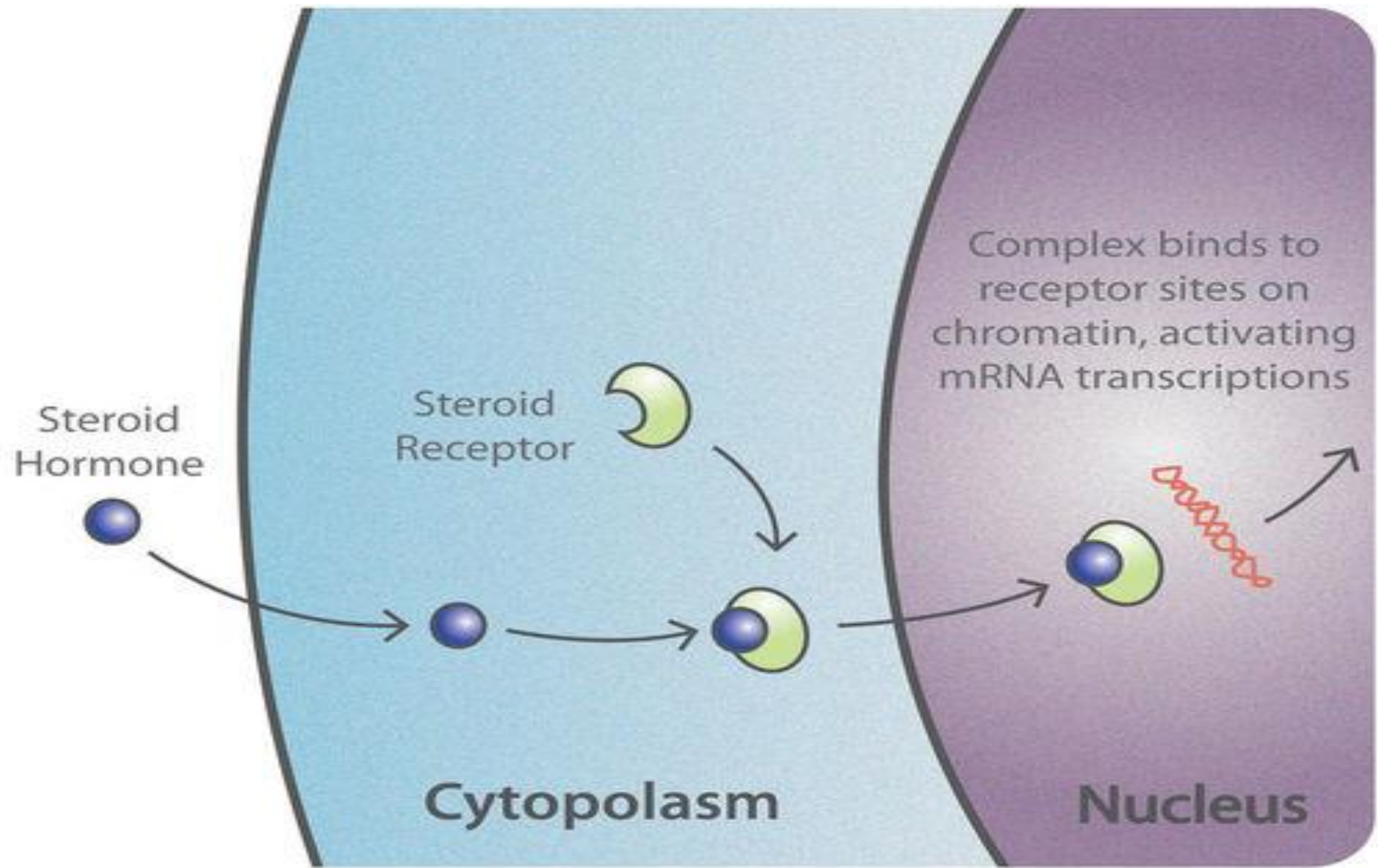
Key Points

- Hormones are released into the bloodstream through which they travel to target sites.
- The target cell has receptors specific to a given hormone and will be activated by either a lipid-soluble (permeable to plasma membrane) or water-soluble hormone (binds to a cell-surface receptor).
- Lipid-soluble hormones diffuse through the plasma membrane to enter the target cell and bind to a receptor protein.
- Water-soluble hormones bind to a receptor protein on the plasma membrane of the cell.
- Receptor stimulation results in a change in cell activity, which may send feedback to the original hormone-producing cell.

- A hormone is a chemical messenger that enables communication between cells. Hormones are secreted by the glands of the endocrine system and they serve to maintain homeostasis and to regulate numerous other systems and processes, including reproduction and development.

Hormone Signaling -

- The glands of the endocrine system secrete hormones directly into the extracellular environment. The hormones then diffuse to the bloodstream via capillaries and are transported to the target cells through the circulatory system. This allows hormones to affect tissues and organs far from the site of production or to apply systemic effects to the whole body.
- Hormone-producing cells are typically specialized and reside within a particular endocrine gland, such as thyrocytes in the thyroid gland. Hormones exit their cell of origin through the process of exocytosis or by other means of membrane transport.



- Cellular recipients of a particular hormonal signal may be one of several cell types that reside within a number of different tissues. This is so in the case of insulin, which triggers a diverse range of systemic physiological effects. Different tissue types may also respond differently to the same hormonal signal. As a result, hormonal signaling is elaborate and hard to dissect.
- Hormones activate target cells by diffusing through the plasma membrane of the target cells (lipid-soluble hormones) to bind a receptor protein within the cytoplasm of the cell, or by binding a specific receptor protein in the cell membrane of the target cell (water-soluble proteins). In both cases, the hormone complex will activate a chain of molecular events within the cell that will result in the activation of gene expression in the nucleus.
- The reaction of the target cells may be recognized by the original hormone-producing cells, leading to a down-regulation in hormone production.

Steps of Hormonal Signaling –

- Biosynthesis of a particular hormone in a particular tissue.
- Storage and secretion of the hormone.
- Transport of the hormone to the target cells, tissues, or organs.
- Recognition of the hormone by an associated cell membrane or an intracellular receptor protein.
- Relay and amplification of the received hormonal signal via a signal transduction process.
- Potential feedback to a hormone-producing cell.

Classification of Hormones - Hormones are typically divided into three classes:

- **Peptide:** Hormones that are modified amino acids or short (peptide) or long (protein) chains of amino acids. Additionally, they can contain carbohydrate moieties.
- **Lipid:** Steroid hormones that contain lipids synthesized from cholesterol and eicosanoids that contain lipids synthesized from the fatty acid chains of phospholipids found in the plasma membrane.
- **Monoamine:** Hormones derived from aromatic amino acids such as phenylalanine, tyrosine, and tryptophan.

Mechanism of Action: Hormones with Cell Surface Receptors

Protein and peptide hormones, catecholamines like epinephrine, and eicosanoids such as prostaglandins find their receptors decorating the plasma membrane of target cells.

Binding of hormone to receptor initiates a series of events which leads to generation of so-called **second messengers** within the cell (the hormone is the first messenger). The second messengers then trigger a series of molecular interactions that alter the physiologic state of the cell. Another term used to describe this entire process is **signal transduction**.

Structure of Cell Surface Receptors - Cell surface receptors are integral membrane proteins and, as such, have regions that contribute to three basic domains:

- **Extracellular domains:** Some of the residues exposed to the outside of the cell interact with and bind the hormone - another term for these regions is the ligand-binding domain.
- **Transmembrane domains:** Hydrophobic stretches of amino acids are "comfortable" in the lipid bilayer and serve to anchor the receptor in the membrane.
- **Cytoplasmic or intracellular domains:** Tails or loops of the receptor that are within the cytoplasm react to hormone binding by interacting in some way with other molecules leading to generation of second messengers. Cytoplasmic residues of the receptor are thus the effector region of the molecule.

Cyclic AMP Second Messenger Systems -

- Cyclic adenosine monophosphate (cAMP) is a nucleotide generated from ATP through the action of the enzyme adenylate cyclase. The intracellular concentration of cAMP is increased or decreased by a variety of hormones and such fluctuations affect a variety of cellular processes. One prominent and important effect of elevated concentrations of cAMP is activation of a cAMP-dependent protein kinase called protein kinase A.
- Protein kinase A is nominally in an catalytically-inactive state, but becomes active when it binds cAMP. Upon activation, protein kinase A phosphorylates a number of other proteins, many of which are themselves enzymes that are either activated or suppressed by being phosphorylated. Such changes in enzymatic activity within the cell clearly alter its state.

Mechanism of action of glucagon:

- Glucagon binds its receptor in the plasma membrane of target cells (hepatocytes).
- Bound receptor interacts with and through a set of G proteins, turns on adenylate cyclase, which is also an integral membrane protein.
- Activated adenylate cyclase begins to convert ATP to cyclic AMP resulting in an elevated intracellular concentration of cAMP.
- High levels of cAMP in the cytosol make it probable that protein kinase A will be bound by cAMP and therefore catalytically active.
- Active protein kinase A runs around the cell adding phosphates to other enzymes, thereby changing their conformation and modulating their catalytic activity and the cell has been changed.
- Levels of cAMP decrease due to destruction by cAMP-phosphodiesterase and the inactivation of adenylate cyclase.

Tyrosine Kinase Second Messenger Systems -

- The receptors for several protein hormones are themselves protein kinases which are switched on by binding of hormone. The kinase activity associated with such receptors results in phosphorylation of tyrosine residues on other proteins. Insulin is an example of a hormone whose receptor is a tyrosine kinase.
- The hormone binds to domains exposed on the cell's surface, resulting in a conformational change that activates kinase domains located in the cytoplasmic regions of the receptor. The activated receptor phosphorylates a variety of intracellular targets, many of which are enzymes that become activated or are inactivated upon phosphorylation.

Fate of the Hormone-Receptor Complex –

- Normal cell function depends upon second messenger cascades being transient events. Indeed, a number of cancers are associated with receptors that continually stimulate second messenger systems. One important part of negative regulation on hormone action is that cell surface receptors are internalized. In many cases, internalization is stimulated by hormone binding.
- Internalization occurs by endocytosis through structures called coated pits. The resulting endosomes may fuse with lysosomes, leading to destruction of the receptor and hormone. In other cases, it appears that the hormone dissociates and the receptor is recycled by fusion of the endosome back into the plasma membrane.