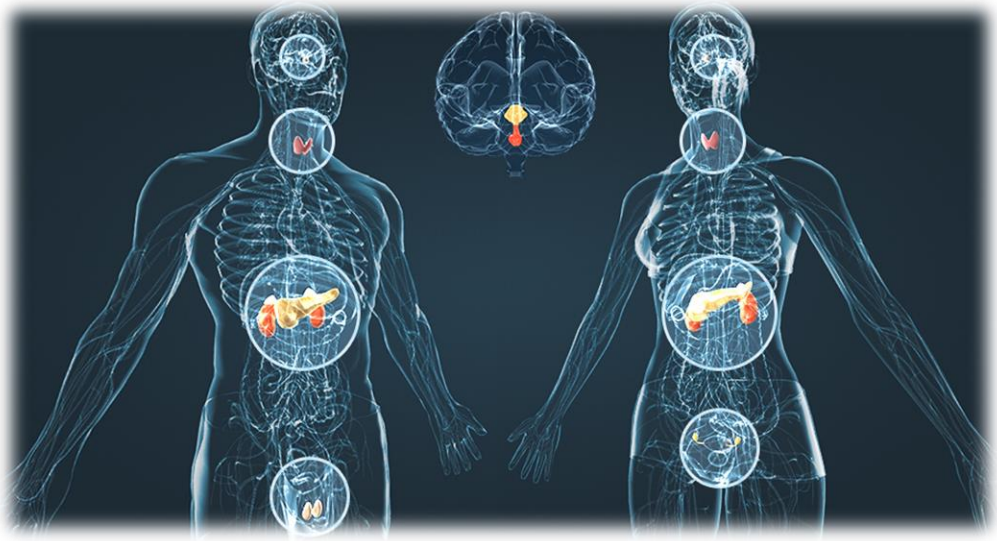

Introduction to Endocrine System Physiology-II

Endocrine System and Disorders (MED321)
Year 3-Semester 1

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HORMONE RECEPTORS AND SIGNAL TRANSDUCTION

- Hormones produce their biologic effects by **binding to specific receptors in target cells**.
- The type of the receptor to which hormones bind is largely determined by the **hormone’s chemical structure**.

Hormone receptors

Plasma membrane receptors

Intracellular Receptors

In the cytoplasm

In the nucleus

Peptides and catecholamines

- Unable to cross the cell membrane
- Bind to **cell membrane receptors**
- Exeption: Thyroid hormones

Steroid hormones

- Lipid soluble
- Cross the plasma membrane
- Bind to **intracellular receptors**.

Channel coupled receptors:

Ligand-gated ion channels (ionotropic receptors)

- Functionally coupled to ion channels
- Hormone binding to these receptors produces a conformational change that opens ion channels on the cell membrane, producing ion fluxes in the target cell
- The cellular effects ocur within seconds of hormone binding

Enzyme coupled receptors:

Catalytic receptors

- Cytosolic domains have intrinsic enzymatic activity or are directly associated with an enzyme.
- Usually contain one transmembrane segment.
- Binding of the ligand causes conformational change in the receptor, inducing enzymatic activity.
- The effect is direct.
- Activated enzyme causes target response

Enzyme coupled receptors:
Catalytic receptors

5 main types of catalytic receptors in mammalian cells.

- **Receptor tyrosine kinases**
- Tyrosine-kinase-associated receptors (Non-receptor tyrosine kinases)
- Receptor serine / threonine kinases
- Receptor guanylate kinases
- Receptor tyrosine phosphatases

Many extracellular signal proteins (insulin, EGF, FGF, HGF, VEGF, IGF1, MCSF, NGF etc.) show their effects through RTKs.

The 2 main enzymes that interact with Gα subunit:

1. **Adenilate cyclase**

- $G\alpha_s$ ve $G\alpha_i$
- ATP → cAMP

The 2 main enzymes that interact with Gα subunit:

1. **Phospholipase C (PLC)**

- ✓Fosfolipaz C (PLC): **$G\alpha_q$**
- ✓PIP_2 → DAG + IP_3
- ✓Oxytocin uses Ca^{2+} as a signaling molecule

The Number and Sensitivity of Hormone Receptors Are Regulated

Receptor modulation: up-regulation and downregulation.

In the context of hormones,

- **Up-regulation** is an increase in the number of a hormone's receptors in a cell, often resulting from a prolonged exposure to a low concentration of the hormone.
  - This has the effect of increasing target-cell responsiveness to the hormone.
- **Down-regulation** is a decrease in receptor number, often from exposure to high concentrations of the hormone.
  - This temporarily decreases target-cell responsiveness to the hormone, thereby preventing overstimulation.

Down-regulation of the receptors: decreases the target tissue's responsiveness to the hormone

- ✓ temporary sequestration of the receptor to the inside of the cell, away from the site of action of hormones that interact with cell membrane receptors
- ✓ destruction of the receptors by lysosomes after they are internalized
- ✓ inactivation of some of the receptor molecules
- ✓ inactivation of some of the intracellular protein signaling molecules;
- ✓ decreased production of the receptors

In some cases, **hormones can down-regulate** or **up-regulate** not only their own receptors but **the receptors for other hormones** as well.

- If one hormone induces down-regulation of a second hormone's receptors, the result will be a reduction of the second hormone's effectiveness: **Antagonism**
  - e.g. Progesterone (a hormone secreted during pregnancy that decreases contractions of the uterus) inhibits uterine responsiveness to estrogen
- On the other hand, a hormone may induce an increase in the number of receptors for a second hormone. In this case, the effectiveness of the second hormone is increased: **Permissiveness**
- **Synergism** occurs when the actions of several hormones are complementary and their effect is greater than the sum of their separate effects
  - E.g. Presence of FSH and Testosterone for effective spermatogenesis

- **Permissiveness** means that hormone A must be present in order for hormone B to exert its full effect.
- A low concentration of hormone A is usually all that is needed for this permissive effect, which may be due to A’s ability to up-regulate B’s receptors.

Abnormal endocrine function

Excess or deficiency in hormone action

- ✓ Abnormal production of a given hormone (excess/insufficient amounts)
- ✓ Decreased receptor number and function.

CONTROL OF HORMONE RELEASE

Patterns of Hormone Secretion

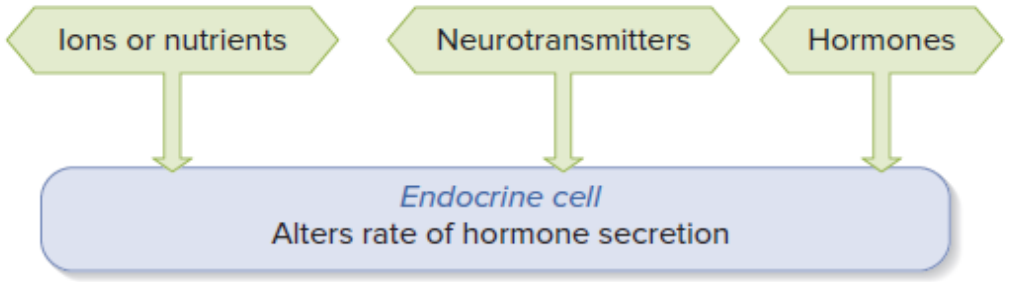
- Chronic hormone regulation. Maintenance of relatively constant concentration of hormone. Thyroid hormone.

- Acute hormone regulation. Epinephrine in response to stress.

- Episodic (Cyclic) hormone regulation. Female reproductive hormones.

- Most hormones are not secreted at constant rate, but their secretion is regulated by 3 different inputs to the endocrine cells.

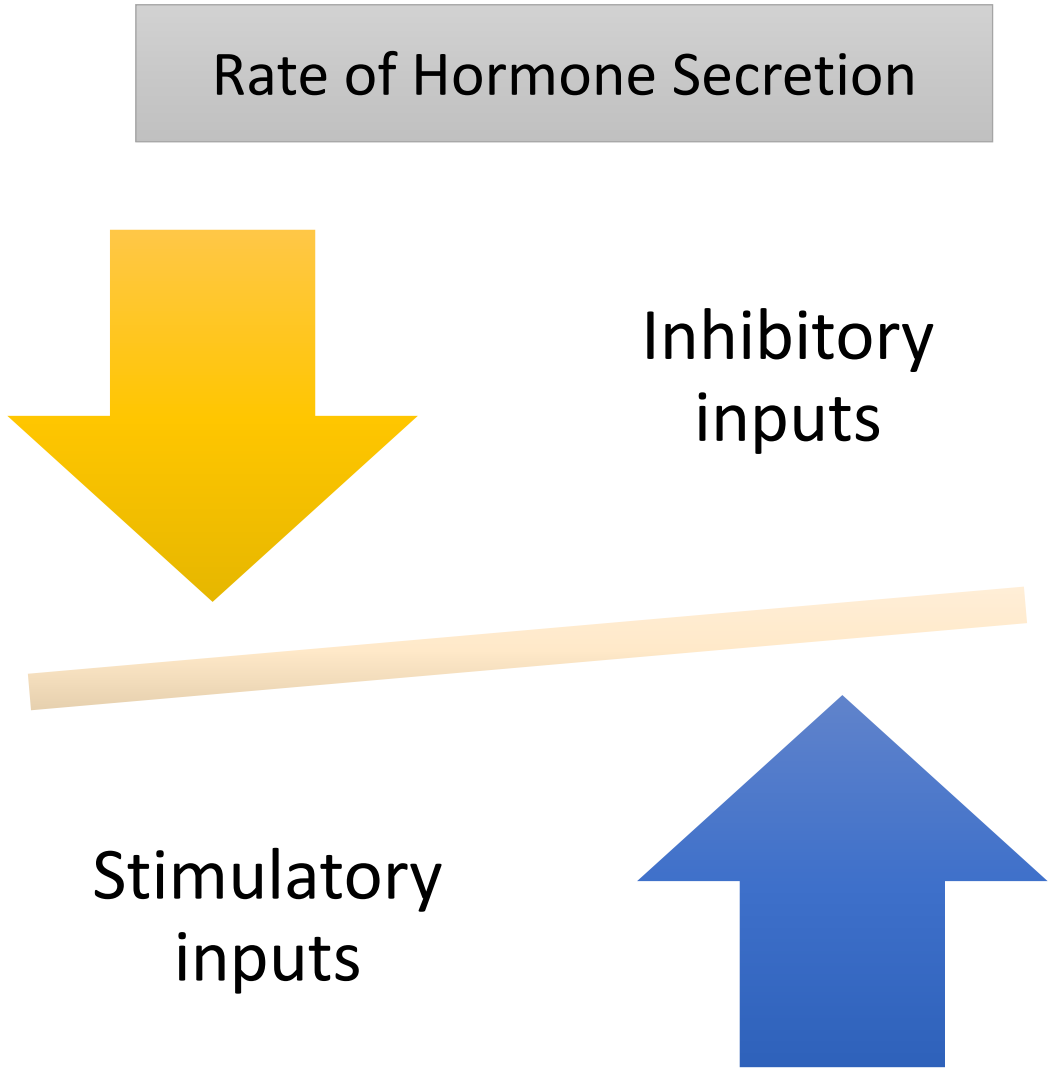
1) Neurotransmitters released from neurons ending on the endocrine cell (**NEURAL CONTROL**)
2) Another hormone (or, in some cases, a paracrine substance) acting on the endocrine cell (**HORMONAL CONTROL**)
3) Changes in the plasma concentrations of mineral ions or organic nutrients



More than one input may influence hormone secretion

Insulin
Glucose and nutrients
Different branches of the autonomic nervous system

The control of endocrine cells illustrates the general principle of physiology that **most physiological functions are controlled by multiple regulatory systems**, often **working in opposition**.



Primarily by **negative feedback** mechanism

1. Neural Control

- Endocrine function is under tight regulation by the nervous system: **Neuroendocrine**
- Hormone release by endocrine cells can be modulated by
  - Postganglionic neurons from the SNS and PSNS using Ach or NE as neurotransmitters
  - Preganglionic neurons using Ach as neurotransmitter

2. Hormonal Control

- In some cases, the endocrine gland is itself a target organ for another hormone
- When the outcome is stimulation of hormone release, the hormone that exerts that effect is referred to as **tropic hormones**.
  - They are all released from the **anterior pituitary gland** (adenohypophysis)
  - Thyroid gland and adrenal cortex

    e.g. regulation of glucocorticoid release by ACTH

- Hormones can also **supress** another hormone's release.
  - Inhibition of GH release by somatostatin
- Hormonal inhibition of hormone release plays an important role in the process of negative feedback regulation of hormone release
- Hormones can stimulate the release of a second hormone in what is known as a **feed-forward mechanism**

3. Control by Plasma Concentraations of Mineral Ions or Organic Nutrients

- The secretion of several hormones is directly controlled—at least in part—by the plasma concentrations of specific mineral ions or organic nutrients
- In each case, a major function of the hormone is to regulate through negative feedback the plasma concentration of the ion or nutrient controlling its secretion.
- Insulin secretion is stimulated by an increase in plasma glucose concentration.
- Insulin, in turn, acts on skeletal muscle and adipose tissue to promote facilitated diffusion of glucose across the plasma membranes into the cytosol.
- Consequently, the action of insulin restores plasma glucose concentration to normal.

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