College of pharmacy

Biochemistry I third stage

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Lecture 4

Biochemistry of Endocrine System

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The nervous and endocrine systems are the two major regulatory systems of the body, and together they regulate and coordinate the activity of essentially all other body structures. The endocrine system is composed of glands that secrete chemical signals into the circulatory system. In contrast, exocrine glands have ducts that carry their secretions to surfaces. The secretary products of endocrine glands are called hormones.

Traditionally, a **hormone** is defined as a chemical signal, or ligand that synthesized in one organ and transported by the circulatory system to act on another tissue. However, this original description is too restrictive because hormones can act on adjacent cells (paracrine action) and on the cell in which they were synthesized (autocrine action) without entering the systemic circulation.

Target cell

The hormone can affect several different cell types; that more than one hormone can affect a given cell type; and that hormones can exert many different effects in one cell or in different cells. The definition of a target includes any cell in which the hormone (ligand) binds to its receptor, whether or not a biochemical or physiologic response has yet been determined.

Hormone receptors

Hormones are present at very low concentrations in the extracellular fluid, generally in the range of **10^{-15} to 10^{-9} mol/L**. This concentration is much lower than that of the many structurally similar molecules (amino acids, peptides, proteins) and other molecules. Target cells, therefore, must distinguish not only

between different hormones present in small amounts but also between a given hormone.

This high degree of discrimination is provided by cell associated recognition molecules called **receptors**. Hormones initiate their biologic effects by binding to specific receptors, and terminate its actions when the effecter dissociates from the receptor. Several biochemical features of this interaction are important in order for hormone receptor interactions to be physiologically relevant:

1. Binding should be specific.
2. Binding should be saturable.
3. Binding should occur within the concentration range of the expected biologic response.

Recognition and coupling domains of receptors

Several classes of peptide hormone receptors have been defined. All receptors have at least two functional domains. A recognition domain binds the hormone ligand and a second region generates a signal that couples hormone recognition to some intracellular function. Coupling (signal transduction) occurs in two general ways.

Polypeptide and protein hormones and the catecholamines bind to receptors located in the plasma membrane and thereby generate a signal that regulates various intracellular functions, often by changing the activity of an enzyme. In contrast, steroid, retinoid, and thyroid hormones interact with intracellular receptors, and it is this ligand receptor complex that directly provides the signal, generally to specific genes whose rate of transcription is thereby affected. **The dual functions of binding and coupling ultimately define a receptor**. This dual purpose distinguishes the target cell receptor from the plasma carrier proteins that bind hormone but do not generate a signal.

Classification of hormones

Hormones can be classified according to the **general features of hormone** and **location of receptors**. The hormones in **group I** are **lipophilic**. After secretion, these hormones associate with plasma transport or carrier proteins, a process that circumvents the problem of solubility while prolonging the plasma half-life of the hormone. The free hormone, which is the biologically active form, readily traverses the lipophilic plasma membrane of all cells and encounters receptors in either the cytosol or nucleus of target cells. The ligand-receptor complex is assumed to be the intracellular messenger in this group.

The hormones in **group II** are **water soluble** that bind to the plasma membrane of the target cell. Hormones that bind to the surfaces of cells communicate with intracellular metabolic processes through intermediary molecules called **second messengers** (the **hormone** itself is the **first messenger**), which are generated as a consequence of the ligand receptor interaction.

Classification of hormones according to general features of hormone

	Group I	Group II
Types	Steroids, iodothyronines, calcitriol, retinoids	Polypeptides, proteins, glycoproteins, catecholamines
Solubility	Lipophilic	Hydrophilic
Transport proteins	Yes	No
Plasma half-life	Long (hours to days)	Short (minutes)
Receptor	Intracellular	Plasma membrane
Mediator	Receptor-hormone complex	cAMP, cGMP, Ca^{2+}, metabolites of complex phosphoinositols, kinase cascades

Classification of hormones according to location of receptors

1	**Group I**	**Hormones that bind to intracellular receptors**
Androgens, Calcitriol, Estrogens, Glucocorticoids, Mineralocorticoids, Progestins, Retinoic acid and Thyroid hormones (T3 and T4)		
2	**Group II**	**Hormones that bind to cell surface receptors**
A	**Group II.A**	**The second messenger is cAMP**
α2- and β-Adrenergic catecholamines, Adrenocorticotropic hormone (ACTH), Antidiuretic hormone (ADH), Calcitonin, Chorionic gonadotropin (CG), human Corticotropin-releasing hormone (CRH), Follicle-stimulating hormone (FSH), Glucagon, Luteinizing hormone (LH), Melanocyte-stimulating hormone (MSH), Parathyroid hormone (PTH) and Thyroid-stimulating hormone (TSH)		
B	**Group II.B**	**The second messenger is cGMP**
Atrial natriuretic factor (ANF)		
C	**Group II.C**	**The second messenger is calcium or phosphatidylinositols (or both)**
Acetylcholine (muscarinic), α1-Adrenergic catecholamines, Angiotensin II, Antidiuretic hormone (vasopressin), Gonadotropin-releasing hormone (GRH), Oxytocin and Thyrotropin-releasing hormone (TRH)		
D	**Group II.D**	**The second messenger is a kinase or phosphatase cascade**
Erythropoietin, Growth hormone (GH), Insulin and Prolactin		

Chemical diversity of hormones

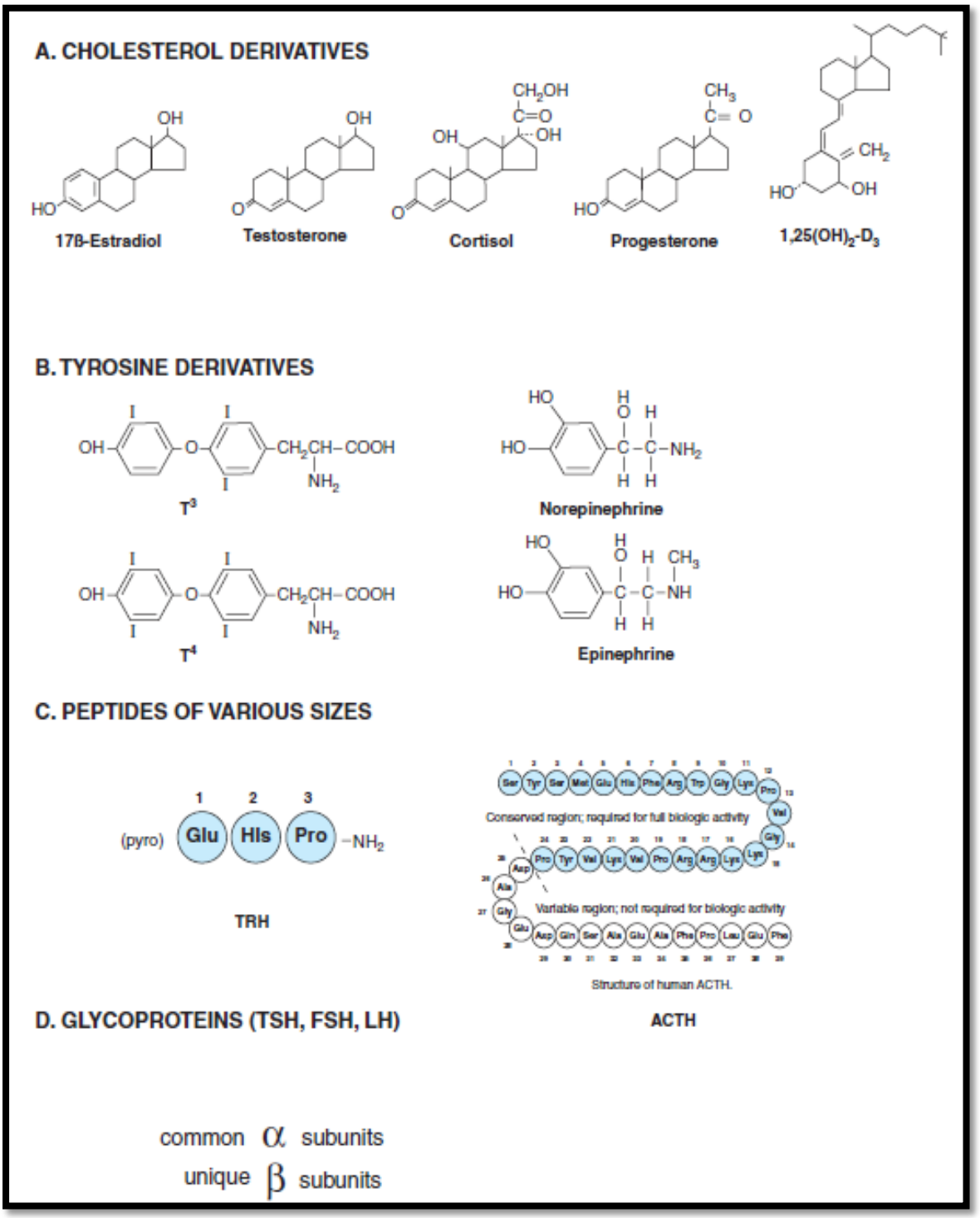
Hormones are synthesized from a wide variety of chemical building blocks.

A. Cholesterol derivative: A large series is derived from cholesterol. These include the glucocorticoids, mineralocorticoids, estrogens, progestins, testosterone and 1,25$(OH)_2$-D_3.

B. Amino acid derivative: The amino acid tyrosine is the starting point in the synthesis of the catecholamines and of the thyroid hormones tetraiodothyronine (thyroxine; T_4) and triiodothyronine (T_3).

C. Peptides of various size: Many hormones are polypeptides. These range in size from thyrotropin-releasing hormone (TRH), a tripeptide, to single chain polypeptides like adrenocorticotropic hormone (ACTH; 39 amino acids), parathyroid hormone (PTH; 84 amino acids), and growth hormone (GH; 191 amino acids). Insulin is an AB chain heterodimer of 21 and 30 amino acids, respectively.

D. Glycoproteins: Follicle-stimulating hormone (FSH), luteinizing hormone (LH), thyroid-stimulating hormone (TSH), and chorionic gonadotropin (CG) are glycoprotein hormones of **αβ heterodimeric structure**. The **α chain is identical** in all of these hormones, and **distinct β chains impart hormone uniqueness**.



Chemical diversity of hormones

Control of hormone secretion

1. The action of a substance other than a hormone: for example: the influence of blood glucose on insulin secretion from the pancreas. An increasing blood glucose level causes an increase in insulin secretion from the pancreas.

Insulin increases glucose movement into cells, resulting in a decrease in blood glucose levels, which in turn causes a decrease in insulin secretion. Thus insulin levels increase and decrease in response to changes in blood glucose levels.

2. Neural control: for example: the neural control of epinephrine and norepinephrine secretion from the adrenal gland. In response to stimuli such as stress or exercise, the nervous system stimulates the adrenal gland to secrete epinephrine and norepinephrine, which help the body respond to the stimuli. When the stimuli are no longer present, secretion of epinephrine and norepinephrine decreases.

3. Feedback: for example: thyroid releasing hormone (TRH) from the hypothalamus the brain stimulates the secretion of thyroid stimulating hormone (TSH) from the anterior pituitary gland, which, in turn, stimulates the secretion of thyroid hormones from the thyroid gland. A **negative feedback** regulation for regulating thyroid hormone secretion exists because thyroid hormones can inhibit the secretion of TRH and TSH. Thus, the concentrations of TRH, TSH, and thyroid hormone increase and decrease within a normal range.

A few examples of **positive feedback** regulation in the endocrine system exist. Prior to ovulation, estrogen from the ovary stimulates luteinizing hormone (LH) secretion from the anterior pituitary gland. LH, in turn, stimulates estrogen secretion from the ovary. Consequently, blood levels of estrogen and LH increase prior to ovulation.

4. Inherent rhythms (circadian rhythm): Adrenocorticotrophic hormone (**ACTH**) is secreted episodically, each pulse being followed 5-10 min later by **cortisol** secretion. These episodes are most frequent in the early morning (between the fifth and eighth hour of sleep) and least frequent in the few hours before sleep. Plasma **cortisol** concentrations are usually **highest** between about **07.00** and **09.00** hour and **lowest** between **23.00** and **04.00** hour.

Endocrine Gland and Hormone	Target Tissue	Principal Actions
POSTERIOR LOBE OF PITUITARY		
Antidiuretic hormone (ADH)	Kidneys	Stimulates reabsorption of water; conserves water
Oxytocin	Uterus	Stimulates contraction
	Mammary glands	Stimulates milk ejection
ANTERIOR LOBE OF PITUITARY		
Growth hormone (GH)	Many organs	Stimulates growth by promoting protein synthesis and fat breakdown
Adrenocorticotropic hormone (ACTH)	Adrenal cortex	Stimulates secretion of adrenal cortical hormones such as cortisol
Thyroid-stimulating hormone (TSH)	Thyroid gland	Stimulates thyroxine secretion
Luteinizing hormone (LH)	Gonads	Stimulates ovulation and corpus luteum formation in females; stimulates secretion of testosterone in males
Follicle-stimulating hormone (FSH)	Gonads	Stimulates spermatogenesis in males; stimulates development of ovarian follicles in females
Prolactin (PRL)	Mammary glands	Stimulates milk production
Melanocyte-stimulating hormone (MSH)	Skin	Stimulates color change in reptiles and amphibians; unknown function in mammals
THYROID GLAND		
Thyroxine (thyroid hormone)	Most cells	Stimulates metabolic rate; essential to normal growth and development
Calcitonin	Bone	Lowers blood calcium level by inhibiting loss of calcium from bone
PARATHYROID GLANDS		
Parathyroid hormone	Bone, kidneys, digestive tract	Raises blood calcium level by stimulating bone breakdown; stimulates calcium reabsorption in kidneys; activates vitamin D

Endocrine Gland and Hormone	Target Tissue	Principal Actions
ADRENAL MEDULLA		
Epinephrine (adrenaline) and norepinephrine (noradrenaline)	Smooth muscle, cardiac muscle, blood vessels	Initiate stress responses; raise heart rate, blood pressure, metabolic rate; dilate blood vessels; mobilize fat; raise blood glucose level
ADRENAL CORTEX		
Aldosterone	Kidney tubules	Maintains proper balance of Na^+ and K^+ ions
Cortisol	Many organs	Adaptation to long-term stress; raises blood glucose level; mobilizes fat
PANCREAS		
Insulin	Liver, skeletal muscles, adipose tissue	Lowers blood glucose level; stimulates storage of glycogen in liver
Glucagon	Liver, adipose tissue	Raises blood glucose level; stimulates breakdown of glycogen in liver
OVARY		
Estradiol	General	Stimulates development of secondary sex characteristics in females
	Female reproductive structures	Stimulates growth of sex organs at puberty and monthly preparation of uterus for pregnancy
Progesterone	Uterus	Completes preparation for pregnancy
	Mammary glands	Stimulates development
TESTIS		
Testosterone	Many organs	Stimulates development of secondary sex characteristics in males and growth spurt at puberty
	Male reproductive structures	Stimulates development of sex organs; stimulates spermatogenesis

Hormone action & signal transduction

Group I hormones interact with an intracellular receptor and group II hormones with receptor recognition sites located on the extracellular surface of the plasma membrane of target cells.

1. Group I hormones

The lipophilic group I hormones diffuse through the plasma membrane of all cells but only encounter their specific, high-affinity intracellular receptors in target cells. These receptors can be located in the cytoplasm or in the nucleus of target cells. The hormone-receptor complex first undergoes an activation reaction. Receptor activation occurs by at least two mechanisms.

For example, **glucocorticoids** diffuse across the plasma membrane and encounter their cognate **receptor in the cytoplasm** of target cells. Ligand-receptor binding results in the dissociation of **heat shock protein 90** (hsp90) from the receptor. This step appears to be necessary for subsequent nuclear localization of the glucocorticoid receptor. This receptor also contains nuclear localization sequences that assist in the **translocation from cytoplasm to nucleus**. The now activated receptor moves into the nucleus and binds with high affinity to a specific DNA sequence called the **hormone response element** (**HRE**). In the case illustrated, this is a **glucocorticoid response element**, or **GRE**. The DNA-bound, liganded receptor serves as a high-affinity binding site for one or more coactivator proteins, and accelerated gene transcription typically ensues when this occurs.

By contrast, certain hormones such as the thyroid hormones and retinoids diffuse from the extracellular fluid across the plasma membrane and go directly into the nucleus. In this case, the cognate receptor is already bound to the HRE (the thyroid hormone response element [TRE], in this example). However, this DNA-bound receptor fails to activate transcription because it is complexed with a

corepressor. Indeed, this receptor corepressor complex serves as an active repressor of gene transcription. The association of ligand with these receptors results in dissociation of the corepressor. The liganded receptor is now capable of binding one or more coactivators with high affinity, resulting in the activation of gene transcription.

2. Group II hormones

The mechanism of action of this group of hormones can best be discussed in terms of the intracellular signals they generate. These signals (second messengers) include **cAMP**, a nucleotide derived from ATP through the action of adenylyl cyclase; **cGMP**, a nucleotide formed by guanylyl cyclase; **Ca^{2+}**; and **phosphatidylinositides**.

G protein-coupled receptors (GPCR)

Many of the group II hormones bind to receptors that couple to effectors through a **GTP-binding protein intermediary**. In the **absence** of hormone, the **G-protein complex** is in an **inactive** guanosine diphosphate **(GDP)-bound form** and is probably not associated with the receptor. On **binding** of hormone to the receptor, there is a presumed conformational change of the receptor and **activation of the G-protein complex**. This results from the exchange of **GDP** with guanosine triphosphate (**GTP**) and activates the effector. The effector can be adenylyl cyclase, Ca^{2+}, Na^{+}, or Cl^{-} channels or it could be a K^{+} channel, phospholipase, or cGMP phosphodiesterase.

A. Cyclic AMP

The hormone is the "first messenger." Hormone combines with receptors on the plasma membrane of the target cell. The plasma membrane has **G-protein** linked receptors. **G protein** releases **GDP** and then binds with **GTP**. Binding **GTP** produces a conformational change in the **G protein** and binds it to **adenylyl cyclase**, an enzyme embedded in the plasma membrane. The activated adenylyl

cyclase catalyzes the **conversion of ATP to cyclic AMP**, cAMP, a secondary messenger. The cAMP activates one or more enzymes **protein kinases** in the cytosol that alter the activity of the cell. **Protein kinases** phosphorylate a specific protein. These activated proteins then trigger a chain reaction leading to a metabolic effect. In the **absence** of a signal, e.g. epinephrine, cAMP is quickly converted to AMP by the enzyme phosphodiesterase.

B. Cyclic GMP

Cyclic GMP (secondary messenger) is made from GTP by the enzyme guanylyl cyclase, which exists in soluble and membrane bound forms. Atrial natriuretic factor increase cGMP by activating the soluble form of guanylylcyclase, and inhibiting of cGMP phosphodiesterase. The increased cGMP activates cGMP dependent protein kinase (PKG), which in turn phosphorylates a number of smooth muscle proteins. Presumably, this is involved in relaxation of smooth muscle and vasodilation.

C. Calcium ions and inositol triphosphate

Cytosolic Ca^{2+} concentration increase by several signals like neurotransmitters, some hormones, and growth factors. Ca^{2+} is a common **second messenger**. Increasing the concentration of Ca^{2+} brings about many cell responses, e. g. muscle contraction, cell division and secretion of certain substances. The concentration of Ca^{2+} is much lower in the cytosol than in the extracellular environment of the cell. Ca^{2+} are actively concentrated in the ER and sometimes into the mitochondria. **Hormone receptor complex** activates the **G protein**. G proteins then activate the membrane bound enzyme phospholipase C. Phospholipase C splits the phospholipid into IP_3 (inositol triphosphate) and **DAG** (diacylglycerol). Both act as **second messengers**. IP_3 stimulates the ER to release **calcium**, which combines with calmodulin in the cytosol of the cell. **Calmodulin-Ca complex** stimulates protein kinase C to phosphorylate certain

proteins. Calcium is a **third messenger** in this case. The activated calmodulin then activates certain enzymes.

D. Protein kinase

The **insulin** and **IGF-I** receptors contain intrinsic ligand activated tyrosine kinase activity. Several **receptors** generally those involved in binding ligands involved in growth control, differentiation, and the inflammatory response either have intrinsic tyrosine kinase activity or are associated with proteins that are tyrosine kinases. Another distinguishing feature of this class of hormone action is that these kinases preferentially phosphorylate tyrosine residues. A third distinguishing feature is that the ligand-receptor interaction that results in a tyrosine phosphorylation event initiates a cascade that may involve several protein kinases, phosphatases, and other regulatory proteins.