Principles of Endocrinology

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Endocrinology is a branch of biology and medicine dealing with the endocrine system, its diseases, and its specific secretions called hormones.
Function of Endocrine system

- Endocrine system, composed of endocrine gland (classical) and cells (non-classical), independently or along with nervous system and immune system, coordinate complex body functions, such as metabolism, growth and development, reproduction etc.
Endocrine glands and organs containing endocrine cells

Major endocrine glands:
- Hypothalamus
- Pineal gland
- Pituitary gland
- Thyroid gland
- Parathyroid glands

Organs containing endocrine cells:
- Thymus
- Heart
- Liver
- Stomach
- Kidney
- Small intestine

Additional organs:
- Adrenal glands
- Testes
- Pancreas
- Kidney
- Ovaries
Endocrine and Exocrine

**Endocrine**

- Endocrine cells
- Ductless
- Well vascularised
- Secret hormones into extracellular fluid or blood

**Exocrine**

- hormone
- Blood flow
- Duct
- Sweat gland

Endocrine gland

- Ductless
- Well vascularised
- Secret hormones into extracellular fluid or blood
Endocrine and neuroendocrine: a chemical released by a specialized group of cells into the circulation and acting on a distant target tissue.

Paracrine: chemical communication between neighboring cells within a tissue or organ.

Autocrine: a chemical acts on the same cell

Intracrine: a chemical acting within the same cell.
Outlines

- Part 1: Introduction of hormone
- Part 2: Hypothalamus, pituitary and their hormones
- Part 3: Regulation of hormones secretion
- Part 4: Endocrine diseases
Functional chemical messengers in endocrine system

- Definition and characteristics
- Hormone secretion and transport
- Mechanisms of hormone actions
Definition of Hormone

- Hormone is **bioactive chemical messenger** released from endocrine cells, and carried by **extracellular fluid or blood** to target cells throughout the body. By binding to its **receptor**, hormone initiates multiple reactions.
Characteristics of hormone

- Specificity
- Signaling
- High effective
- Cooperation
Chemical classification of hormones

- **Amino acid derivatives**
  - Dopamine, catecholamines, and thyroid hormone

- **Small neuropeptides**
  - Gonadotropin-releasing hormone (GnRH), thyrotropin-releasing hormone (TRH), somatostatin, and vasopressin

- **Large proteins**
  - Insulin, luteinizing hormone (LH), and parathyroid hormone (PTH)

- **Steroid hormones**
  - Cortisol, estrogen

- **Vitamin derivatives**
  - Retinoids (vitamin A) and vitamin D
Structure of hormones

Protein and Peptide Hormones
- Prohormone
- Endothelin
- Insulin
  - B Chain
  - H$_2$N
  - A Chain

Steroid Hormones
- Cholesterol
- Steroid Nucleus

Tyrosine Derivatives
- Thyroxine
- Epinephrine
Hormone synthesis and processing – peptide hormones

1. Transcription

- Transcription factors
- RNA
- DNA
- Promoter Region

2. Post-transcriptional modifications

- Mature RNA
- Intron sequences
- 3' poly A tail

3. Translation

- Protein
- H₂N
- COOH

4. Post-translational modifications

- Peptidases

- Active hormone
- Peptide fragment
Synthesis of most steroid hormones is based on modifications of the precursor - cholesterol.

Multiple regulated enzymatic steps are required for the synthesis of testosterone, estradiol, cortisol, and vitamin D.
Many hormones circulate in association with serum-binding proteins.

- Steroid and thyroid hormones are less soluble in aqueous solution than protein and peptide hormones and over 90% circulate in blood as complexes bound to specific plasma globulins or albumin.

Bound and free hormones are in equilibrium.

- T4 and T3 binding to thyroxine-binding globulin (TBG), albumin, and thyroxine-binding prealbumin (TBPA)
- Cortisol binding to cortisol-binding globulin (CBG)
Transport of hormones in the circulation

- Unbound or free hormone is biologically active.
- Hormone binding delays metabolism and provides a circulating reservoir of hormones.
- Alterations in the serum concentrations of binding proteins alter total serum concentrations of a hormone but may have much less effect on the concentrations of free hormone.
Half-lives of hormones

- The half life ($t^{1/2}$) of catecholamines is in the order of seconds, minutes for protein and peptide hormones and hours for steroid and thyroid hormones.

- An understanding of circulating hormone half-life is important for achieving physiologic hormone replacement.
  - T4 has a half-life of 7 days. >1 month is required to reach a new steady state, but single daily doses are sufficient to achieve constant hormone levels.
  - T3 has a half-life of 1 day. Its administration is associated with more dynamic serum levels and it must be administered two to three times per day.
Functions of hormones

◆ Growth
  • GH
  • IGF-1
  • Thyroid hormone
  • Sex steroids

◆ Reproduction
  • Sex determination and sexual maturation
  • Conception, pregnancy, lactation and child-rearing

◆ Maintenance of homeostasis
Hormones and homeostasis

- **Thyroid hormone** - controls about 25% of basal metabolism in most tissues
- **Cortisol** - exerts a permissive action for many hormones in addition to its own direct effects
- **PTH** - regulates calcium and phosphorus levels
- **Vasopressin** - regulates serum osmolality by controlling renal free water clearance
- **Mineralocorticoids** - control vascular volume and serum electrolyte (Na+, K+) concentrations
- **Insulin** - maintains euglycemia in the fed and fasted states
Mechanisms of hormone action

- **Step 1:** Binding to receptors
- **Step 2:** Intracellular signaling cascade
- **Step 3:** Final physiological response
Hormone receptors

- **Cell-surface membrane receptors**
  - Amino acid derivatives and peptide hormones
- **Intracellular nuclear receptors**
  - Steroids, thyroid hormones, vitamin D, and retinoids
Membrane Receptor Families

- **G protein–coupled seven-transmembrane receptor (GPCR)**
  - β-Adrenergic, LH, FSH, TSH, Glucagon, PTH, PTHrP, ACTH, MSH, GHRH, CRH, α-Adrenergic, Somatostatin, TRH, GnRH

- **Receptor tyrosine kinase**
  - Insulin, IGF-I, EGF, NGF

- **Cytokine receptor–linked kinase**
  - GH, PRL

- **Serine Kinase**
  - Activin, TGF-β, MIS
G-protein linked receptors that frequently activate serine/threonine kinases through second messengers such as cAMP, diacylglycerol, calmodulin
G protein–coupled seven-transmembrane receptor (GPCR)

- When hormone binding to the receptor, G protein’s α subunit
  - Releases GDP, binds GTP
  - Dissociates from its β γ subunits & the receptor
  - Binds & activates/inhibits effector (adenyl/guanylate cyclase, phospholipase C)
  - Hydrolyzes GTP to GDP
  - Re-associates with its β γ subunits
Receptor tyrosine kinase

Receptors with inherent tyrosine kinase activity or associated with intracellular molecules possessing tyrosine kinase activity. Some intracellular kinases are attached to the membrane.
Insulin receptor and intracellular signaling pathways in skeletal muscle
Mechanism of thyroid hormone receptor action
Outlines

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- Part 4: Endocrine diseases
Nucleus in Hypothalamus

Specific areas that produce and release multiple hormones
Vasopressin and oxytocin are synthesized in hypothalamus but released in posterior pituitary (green).

Hormones produced in hypothalamus are carried via hypothalamic-hypophysial portal system to anterior pituitary and regulate the endocrine cells' activity in the anterior pituitary (red).
Hypothalamus-pituitary-target glands axes
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Regulation of hormones secretion

- Hormonal rhythms
- Feedback control (Negative and positive)
- Neuroendocrine interactions
- Cross-talk with immune system
Hormonal rhythms

- **Rhythms**
  - circadian
    - light/dark fine/tune endogenous rhythm of cells & suprachiasmatic nucleus of hypothalamus
    - Pituitary hormones, melatonin, cortisol
  - monthly
  - seasonal (day length; atavistic)
  - developmental (puberty, menopause)

- **Pulsations/oscillations**
  - GnRH, gonadotropins
Circadian and pulsatile secretion of ACTH and cortisol
Changes in the ovarian follicle, endometrial thickness, and serum hormone levels during a 28-day menstrual cycle.
**Hormonal rhythms**

- Recognition of these rhythms is important for endocrine testing.

  - The HPA axis exhibits characteristic peaks of ACTH and cortisol production in the early morning, with a nadir during the night.

  - As cortisol is normally high in the morning, morning cortisol levels are similar in Patients with Cushing's syndrome and normal individuals.

  - Patients with Cushing's syndrome characteristically exhibit increased midnight cortisol levels when compared to normal individuals.
Hormonal rhythms

- Recognition of these rhythms is important for glucocorticoids treatment.
  - The HPA axis is more susceptible to suppression by glucocorticoids administered at night as they blunt the early morning rise of ACTH.
  - Glucocorticoid replacement that mimics diurnal production by administering larger doses in the morning than in the afternoon.
Hormonal rhythms

• When relating serum hormone measurements to normal values, one should be aware of the pulsatile nature of hormone secretion and the rhythmic patterns of hormone production.

• Integrated markers have been developed to circumvent hormonal fluctuations.
  • 24-h urine collections for cortisol
  • IGF-I as a biologic marker of GH action
  • HbA1c as an index of long-term blood glucose control
Hypothalamic–pituitary–negative feedback

- Thyroid hormones feedback on the TRH-TSH axis
- Cortisol feedback on the CRH-ACTH axis
- Gonadal steroids feedback on the GnRH-LH/FSH axis
- IGF-I feedback on the GHRH-GH axis
Feedback regulation not involve pituitary

- Calcium feedback on PTH
- Glucose feedback on insulin
- Leptin feedback on hypothalamus
Feedback regulation of Hormones in classic endocrine pathways

Principles of feedback control in the endocrine system
Hypothalamus-pituitary-thyroid axis
Neuroendocrine interactions

• All endocrine glands are innervated by autonomic nerves and these may either directly control their endocrine function and/or regulate blood flow (and hence function) within the gland.

• Hormones, in turn, may affect central nervous system functions such as mood, anxiety and behavior.
Neuroendocrine interactions

- Neurosecretory cells may directly convert a neural signal into a hormonal signal.
- Activation of neurosecretory cells leads to secretion of a hormone into the circulation.
Neuroendocrine interactions

- **Neurosecretory cells include:**
  - Cells that secrete hypothalamic releasing and inhibiting hormones controlling TSH, ACTH, LH and FSH release from the anterior pituitary gland.
  - The hypothalamic neurons the axon terminals of which secrete oxytocin and vasopressin from the posterior pituitary gland.
  - The chromaffin cells of the adrenal medulla (embryologically modified neurons) that secrete epinephrine and norepinephrine into the general circulation.
• The significance of these neurosecretory cells is that they allow the endocrine system to integrate and respond to changes in the external environment.
  • The CRH-ACTH-cortisol axis can be activated by stress generated from external cues
  • Oxytocin secretion by a suckling baby.
Oxytocin & Prolactin
Cross-talk between the endocrine system and the immune system

• Thymic hormones and immunomodulators may alter endocrine function
• Hormones may modulate immune responses.
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Endocrine disease

Endocrine diseases fall into three major categories:

- **Hormone excess**
- **Hormone deficiency**
- **Altered tissue responses to hormones**
  - Hormone resistance, activating mutations of receptors
Hormone excess

- Neoplastic growth of endocrine cells
  - Pituitary adenomas, hyperparathyroidism
- Autoimmune disorders
  - Graves’ disease
- Excess hormone administration
  - Iatrogenic Cushing’s syndrome
- Infectious / inflammation
  - Subacute thyroiditis
Hormone deficiency

- Autoimmunity
  - Hashimoto’s thyroiditis, type 1 diabetes, Addison’s disease
- Iatrogenic
  - Radiation, surgery
- Infection / inflammation
  - Adrenal tuberculosis, hypothalamic sarcoidosis
- Infarction / hemorrhage
  - Sheehan’s syndrome
- Enzyme defects
  - Congenital adrenal hyperplasia
- Nutritional deficiency
  - Iodine deficiency, vitamin D deficiency
Thyroid hormone excess – Graves’ disease
Thyroid hormone deficiency - hypothyroidism

Before (2005)

After (2009)
Growth hormone excess – acromegaly and gigantism

Before

At admission
Addison’s disease

Pro-opiomelanocortin (POMC)

ACTH

αMSH

βMSH

γMSH

Addison's disease:

- Note the generalised skin pigmentation (in a Caucasian patient) but especially the deposition in the palmer skin creases, nails and gums.

- She was treated many years ago for pulmonary TB. What are the other causes of this condition?
Diagnosis of endocrine disease

◆ Principles of diagnosis
  • Functional diagnosis
  • Localization
  • Etiologic/Pathologic diagnosis
Diagnosis is based on the measurement of hormone concentrations in venous serum or body fluids such as urine or saliva.

Interpretation of the results of these assays should always take into account three factors:

- The clinical features of the patient
- The concentration of the variable regulated by the hormone
- The concentration of other hormones in the feedback loop
Correct interpretation of thyroid, adrenal or gonadal hormone concentrations requires the results of the appropriate pituitary hormone concentrations.

- When T3 and T4 concentrations are low, TSH should be evaluated.
  - TSH is elevated – primary hypothyroidism
  - TSH is decreased – secondary hypothyroidism
Factors effect the measurement of hormones

- Gender
- Age
- Pulsatile nature of hormones
- Sleep
- Meals
- Medications
Functional diagnosis – dynamic tests

- When baseline hormone associated with pathologic conditions to overlap with the normal range
  - In situations of suspected endocrine hyperfunction, suppression tests are used
    - The dexamethasone suppression test in Cushing’s syndrome
  - In situations of suspected endocrine hypofunction, stimulation tests are used
    - The ACTH stimulating test in adrenal insufficiency
Feedback regulation of endocrine axes
Treatment of endocrine diseases

- **Endocrine hyperfunction**
  - Removing tumors surgically
  - Reducing hormone levels medically

- **Endocrine hypofunction**
  - Physiologic hormone replacement
Thank you!