GENERAL ENDOCRINOLOGY

Dr.T.L.Upadhyaya
Gandaki Medical College

The main subjects

- **Definition of endocrinology**
- **Hormone classification**
- **Mechanism of hormone action**
- **Regulation of hormone**
- **Disorders of the endocrine system**
- **Laboratory test**
- **Treatment of endocrine diseases**
- **Approach to patient with E.diseases**

Definition of Endocrinology (A)

- **Endocrine: The term *endocrine* refers to the process of secretion of biologically active substances into the body.** This contrasts with the term exocrine, which refers to external secretion, generally via anatomically identifiable ducts, such as into the gastrointestinal tract. As the term is ordinarily used, an endocrine gland or cell is one that secrets substances, referred to as *hormones*, that exert regulatory functions , typically in cells other than those in which they are produced.

Definition of Endocrinology (B)

- **Hormone**: The hormone is a substance that is secreted by one cell and travels through the *circulation*, where it exerts actions on other cells.
- **Receptor**: The receptor is a molecule to which the hormone binds to elicit its actions. A receptor has *two functions*. First, it must be able to distinguish the hormone. A receptor must be capable of binding the hormone with *great affinity* and also must not bind extraneous substances. Second, the receptor must be able to transmit the information gained from the binding to trigger a cellular response.

Definitions of endocrinology (C)

- **Paracrine:** locally released hormones can act on cells in the immediate vicinity of their release. For example, Somatostatin is released by the pancreatic delta cells and has the potential to suppress insulin released by β cells .
- **Autocrine:** Hormones can also act on the cells in which they are produced.

Hormone classification (A)

Hormones are classified into **four major groups** depending on their biochemical structure and methods of synthesis.

- **1. Peptides and proteins**

  Form the great majority of all hormones.

  Include all of the hormones of the hypothalamus, pituitary gland, parathyroid glands, gastrointestinal tract, and pancreas.

Hormone classification (B)

- 2. **Amino acid derivatives**

Small water-soluble compounds derived from amino acids

Hormone derived from tyrosine Include the thyroid hormones(T3 and T4) ,the catecholamines, and dopamine.

Hormone classification (C)

- 3. **Steroids**

Fat-soluble lipids that can pass through plasma membranes but need to circulate bound to plasma proteins, because they are water insoluble.

Derived from cholesterol.

Include hormones of the adrenal cortex, gonads (ovary and testes), and placenta.

Hormone classification (D)

- 4.**Eicosanoids**

Derived from arachidonic acid

Prostaglandin and leukotrienes are the major types.

Mechanism of hormone action

Hormones are transported to all the cells of the body through the circulatory system. The specific response attributed to the hormones must be related to the properties of the cells in the stimulated target tissues. The specificity of the hormone for the cells of its target tissues depends on the fit of the hormone to its receptor. There are two types of mechanisms of hormone action .

Mechanism of hormone action (A)

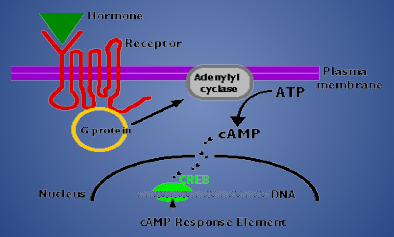
- **Through the cell membrane receptors**

Most peptide 、protein hormone and catecholamine hormones act at the surface of the target cells by binding to a specific receptor on the external membrane of the cell (*cell membrane receptor*),where they stimulate the activity of the enzyme, *adenylcyclase* ,and the production of *cyclic adenosine monophosphate (cAMP).*

Mechanism of hormone action (A)

The function of cAMP is to act as *a"second messenger"* by accepting the information offered by the hormone-receptor complex and transmitting it to its molecular destination within the cell. This is achieved by the activation of protein kinase enzymes in the cell.

Figure1.The mechanism of action of peptides and proteins hormone with cAMP as second messenger



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Mechanism of hormone action (B)

- Through the cytoplasmic receptors steroid and thyroid hormone act for the most part by binding to intracellular receptors.

Steroid hormones are lipid soluble, in addition to their small size ,accounts for their ability to diffuse freely across the cell membrane. Receptors for steroid hormone, located in the cytoplasm of target tissue ,are not attached to cytoplasmic organelles and for this reason they are sometimes referred to as *mobile receptors*.

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Mechanism of hormone action (B)

Steroid hormone cross the cell membrane, and in nontarget tissues, they diffuse freely in and out according to the concentration gradient, but in the target tissue cells they bind with specific cytoplasmic receptor proteins. The steroid receptor complex then translocates to the nucleus where it binds to a specific sites on the DNA or to other transcription factors and induce the new protein produce.

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The action of the steroid hormone

- Steroid hormones pass through the cell membrane of the target cell.
- The steroid hormone binds with a specific receptor in the cytoplasm.
- The receptor bound steroid hormone travels into the nucleus and binds to another specific receptor on the chromatin.
- The steroid hormone-receptor complex calls for the production of messenger RNA (mRNA) molecules, which code for the production of proteins.

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Regulation of hormone

- The relationship between the nervous and endocrinology.
- Hormone release often has rhythmic patterns.
- Specific stimuli received by the endocrine cells cause them to increase their hormone secretion .Some stimuli decrease secretion of hormone
- *Feedback regulation*

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Regulation of hormone(A)

- The relationship between the nervous and endocrinology

The nervous system has evolved to release regulatory substances(neurotransmitters) from nerve terminals that act across synaptic junctions on adjacent cells. These substances may travel considerable distances to act , but when they do so, this generally occurs along the axons.

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Regulation of hormone(A)

The brain is also an endocrine gland, it is the major source of some hormones. The hypothalamic releasing hormone or factors include: thyrotropin releasing hormone(TRH) , corticotropin releasing hormone(CRH), growth hormone releasing hormone(GHRH), gonadotropin releasing hormone (GnRH), somatostatin ,and dopamine .

Regulation of hormone(A)

The Pituitary also can produce main five type hormone, it include :

Adrenocorticotropic hormone (ACTH)

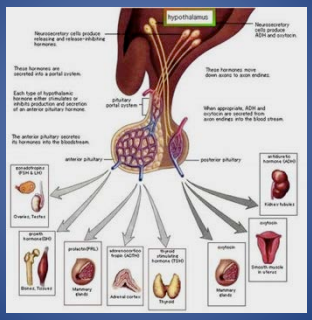
Thyroid stimulating hormone (TSH)

Growth hormone(GH)

Follicle-stimulating hormone(FSH)and luteinizing hormone (LH)

Prolactin (PRL)

Regulation of hormone(A)



Regulation of hormone (B)

- **Hormone release often has rhythmic patterns.**

1). Day-night(circadian)rhythms, e.g. adrenocorticotropic hormone (ACTH), prolactin, GH,TSH.

2). Monthly rhythms, e.g. oestrogen and progesterone have a 28-day cycle, a menstrual cycle.

Regulation of hormone (C)

- **Specific stimuli received by the endocrine cells cause them to increase their hormone secretion .**

1)Nervous stimuli induce adrenaline release in the adrenal medulla.

2)Biochemical stimuli induce the secretion of hormones. e.g. ACTH induces cortisol release from the adrenal cortex.

Regulation of hormone (D)

- **Some stimuli decrease hormone** secretion of hormone ,e.g. somatostatin (GHIH) released by hypothalamus decreases the amount of GH released by anterior pituitary gland.

Regulation of hormone (E)

- The concentration of the secreted hormone in the blood, and /or the effects produced by the hormone , control subsequent secretion of the hormone ,this is called ***feedback loop system***, including ***negative feedback*** (common) and ***positive feedback***.

Regulation of hormone (E)

- ***Negative feedback is the most common type of regulatory loop in biological system*** , **Which means** the level of hormones in circulation or the response produced by the hormone negates or reverses the original stimulus ,decrease the secretion of their stimulating hormone for example ,ACTH stimulates the release of cortisol, cortisol in turn inhibits the ACTH release.

Regulation of hormone (E)

- In some cases , hormonal control system in the body can operate as ***positive feedback systems***, in these systems ,the response augments rather than attenuates the stimulus. Pregnancy is an example of a hormonal positive feedback system, as the fetus grows, the feto-placental unit ,produces increasing amounts of the steroid hormones estrogen and progesterone, these hormones operate in such a way as to maintain the placenta and support pregnancy.

Regulation of hormone (E)

- In conclusion ,A variety of mechanisms regulate circulating hormone levels .a hormone may be regulated by their circadian rhythms、feedback inhibition by hormones of their synthesis and or release、stimulating or inhibiting by other biochemical substances or brain hormone . In some instances complex regulatory networks are present.

Regulation of ACTH

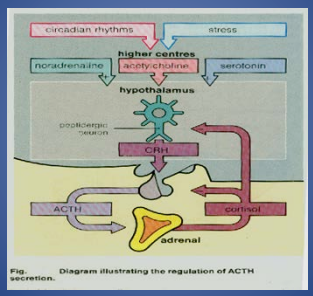


Fig. Diagram illustrating the regulation of ACTH secretion.

Regulation of TSH

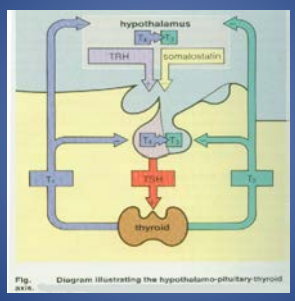
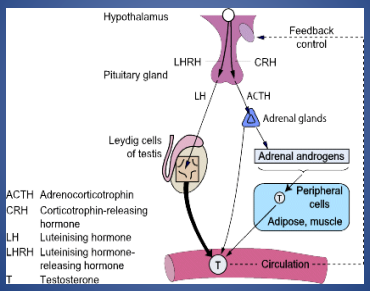


Fig. Diagram illustrating the hypothalamo-pituitary-thyroid axis.

Regulation of Testosterone



Disorders of the endocrine system Hormones deficiency syndromes(A)

- **Hypofunction of Endocrine Glands**

Endocrine glands may be damaged by neoplasia, infections, hemorrhage, autoimmune disorders, and other causes.

A deficiency of a hormone that controls the synthesis and release of another hormone may result in a syndrome, which stimulates a primary deficiency of that target organ. Thus, hypothalamic lesions resulting in impaired secretion of releasing hormones may be manifested by pituitary dysfunction, which in turn may result in abnormal in the function of its various target organs.

Disorders of the endocrine system Hormones deficiency syndromes(B)

- **Hormone Deficiency Secondary to Extraglandular Disorders.**

Extraglandular disorders can result in hormone deficiency.They may involve defective conversion of prohormones to active forms, enhanced degradation of hormone,or the production of substances (antibodies ,hormone antagonists) that block the actions of hormone.

Disorders of the endocrine system Hormones deficiency syndromes(C)

- **Hyporesponsiveness to hormones**

Hormone levels may be normal or even elevated in the presence of manifestations of endocrine deficiency. These conditions may be due to these problems, e.g. antibodies to the insulin receptor and abnormal conversion of testosterone to dihydrotestosterone ;They may also result from decreased ability of the endocrine target gland to respond to hormone.

Disorders of the endocrine system Hormones deficiency syndromes(D)

- **Abnormal Production or Administration of Antagonists**

Rarely, endogenously produce or exogenously administered substances may produce a hormone-resistant state. Antibodies to the insulin receptor may produce a hormone-resistant state.

Disorders of the endocrine system Hormone Excess Syndromes (A)

- **Hyperfunction of Endocrine Glands**

The most common cause of hormone excess syndromes is hyperfunction of endocrine glands secondary to tumors or hyperplasia. Such as hyperfunction of thyroid, adrenals , parathyroids is caused by hyperplasia or tumors.

Disorders of the endocrine system
Hormone Excess Syndromes (B)

- **Ectopic Hormone Production**

  Hormone may be produced in excess by cells of endocrine or nonendocrine origin that are not normally the primary source of a hormone. For example , small-cell lung carcinoma can produce the ACTH ,induce the ectopic ACTH syndrome.

Disorders of the endocrine system
Hormone Excess Syndromes(C)

- Hormone Administration

  Hormone excess states may occur when hormone are used to treat non endocrine disease, hormone replacement therapy is excessive .for example , use cortisol for a long time to treat the autoimmune disease that can let the hypercortisolism happen.

Disorders of the endocrine system
Hormone Excess Syndromes(D)

- Tissue Hypersensitivity

  Endocrine excess syndromes caused by hypersensitivity of target tissues are uncommon. Thyroid hormones increase the catecholamine receptors in certain tissues and this lead to excessive bate-adrenergic stimulation.

Disorders of the endocrine system
Hormone Excess Syndromes(E)

- Autoimmune Disease

  The most frequent situation in which this occurs in thyrotoxicosis.

- Hormone Biosynthetic or metabolic defects

  Certain adrenal steroid biosynthetic defects (the 21a- and 11a- hydroxylase syndrome) result in overproduction of hormone proximal to the block.

Disorders of the endocrine system
Hormone Excess Syndromes(F)

- Secondary Hormone Hypersecretion

  Hypersection of hormone may be due to excessive physiologic stimulation of glands that are basically normal. For example, Secondary hyperinsulinism occurs in obesity.

Disorders of the endocrine system
Multiple Endocrine syndromes (A)

- Multiple endocrine deficiencies

  The most common syndrome of multiple endocrine deficiencies may involve immunologic destruction of pancreatic islets, thyroid, adrenals, and gonads .

Disorders of the endocrine system
Multiple Endocrine syndromes (B)

- Multiple endocrine neoplasia (**MEN**)

At least three syndromes of multiple endocrine hyperfunction result from hyperplasia, adenomas, or carcinomas of endocrine tissues ,termed *multiple endocrine neoplasia (MEN)* which includes three types :type 1,2a,and 2b.

Type1 is associated with Hyperfunction of parathyroid, pancreatic islets and pituitary.

Type2a is associated with pheochromocytoma, medullary carcinoma of thyroid, parathyroid carcinoma.

Type2b is associated with medullary thyroid carcinoma, pheochromocytoma, and other features such as neuromas.

Laboratory Testing

- Hormone level

The hormone level can provide the direct evidence for endocrine disorders, but because the hormones are regulated by various factors ,hormone levels should be evaluated in this context. The significance of hormone levels can sometimes be evaluated only by the simultaneous measurement of more than one hormone.

The level of free rather than total hormone is usually the best index of the effective hormone concentration in plasma.

Laboratory Testing

- Dynamic Testing

Provocative testing assesses the ability of a gland to respond to stimuli as an index of its reserve capacity. This is especially useful when plasma or urinary hormone measurements are borderline.

When endocrine hyperfunction , the inhibition tests can assess the extent to which the normal physiologic mechanisms that control hormone release are suppressed or the degree of autonomy of the hormone – producing tumor or hyperplastic gland.

Treatment of endocrine diseases

- Hormone replacement is given in endocrine deficiency syndrome.
- In hormone-excess syndromes, a variety of approaches are used .For example, hyperfunction tumors are removed , drugs are given to block hormone production, such as propylthiouracil (PTU) for thyrotoxicosis.

Learning main points

- **Definition** : ***Endocrine, Hormone, Receptor, Negative feedback , The second messenger , Multiple endocrine neoplasia (MEN) ,***
- Hormone classification and their action mechanisms
- Hormone regulation.

- Approach to the Patient: Endocrine Disease

- Because endocrinology interfaces with numerous physiologic systems, there is no standard endocrine history and examination. Moreover, because most glands are relatively inaccessible, the examination usually focuses on the manifestations of hormone excess or

- deficiency, as well as direct examination of palpable glands, such as the thyroid and gonads. For these reasons, it is important to evaluate patients in the context of their presenting symptoms, review of systems, family and social history, and exposure to medications that may affect the endocrine system. Astute clinical skills are required

- To detect subtle symptoms and signs suggestive of underlying endocrine disease. For example, a patient with Cushing's syndrome may manifest specific findings, such as central fat redistribution, striae, and proximal muscle weakness, in addition to features seen commonly in the general population, such as obesity,

- plethora hypertension, and glucose intolerance. Similarly, the insidious onset of hypothyroidism—with mental slowing, fatigue, dry skin, and other features—can be difficult to distinguish from similar, nonspecific findings in the general population. Clinical judgment, based on knowledge of disease prevalence and pathophysiology, is

- required to decide when to embark on more extensive evaluation of these disorders. Laboratory testing plays an essential role in endocrinology by allowing quantitative assessment of hormone levels and dynamics. Radiologic imaging tests, such as CT scan, MRI, thyroid scan, and ultrasound, are also used for the diagnosis of endocrine disorders. However, these tests are generally employed only after a hormonal abnormality has been established by biochemical testing.

- Hormone Measurements and Endocrine Testing
- Radioimmunoassays are the most important diagnostic tool in endocrinology, as they allow sensitive, specific, and quantitative determination of steady-state and dynamic changes in hormone concentrations. Radioimmunoassays use antibodies to detect specific hormones. For many peptide hormones, these measurements are now configured to use two different antibodies to increase binding affinity and specificity

- There are many variations of these assays; a common format involves using one antibody to capture the antigen (hormone) onto an immobilized surface and a second antibody, coupled to a chemilumenescent (ICMA) or radioactive (IRMA) signal to detect the antigen. These assays are sensitive enough to detect plasma hormone concentrations in the picomolar to nanomolar range, and they can readily distinguish structurally related

- Proteins such as PTH from PTHrP. A variety of other techniques are used to measure specific hormones, including mass spectroscopy, various forms of chromatography, and enzymatic methods; bioassays are now rarely used.
- Most hormone measurements are based on plasma or serum samples. However, urinary hormone determinations remain useful for the evaluation of some conditions.

- Urinary collections over 24 h provide an integrated assessment of the production of a hormone or metabolite, many of which vary during the day. It is important to assure complete collections of 24-h urine samples; simultaneous measurement of creatinine provides an internal control for the adequacy of collection and can be used to normalize some hormone measurements.

- A 24-h urine free cortisol measurement largely reflects the amount of unbound cortisol, thus providing a reasonable index of biologically available hormone. Other commonly used urine determinations include 17-hydroxycorticosteroids, 17-ketosteroids, vanillylmandelic acid, metanephrine, catecholamines, 5-hydroxyindoleacetic acid, and calcium.

- The value of quantitative hormone measurements lies in their correct interpretation in a clinical context. The normal range for most hormones is relatively broad, often varying by a factor of two- to tenfold. The normal ranges for many hormones are gender- and age-specific. Thus, using the correct normative database is an essential part of interpreting hormone tests. The pulsatile nature of hormones and factors that can affect their secretion, such as sleep, meals, and medications, must also be considered. Cortisol values increase fivefold between midnight and dawn; reproductive hormone levels vary dramatically during the female menstrual cycle.

- For many endocrine systems, much information can be gained from basal hormone testing, particularly when different components of an endocrine axis are assessed simultaneously. For example, low testosterone and elevated LH levels suggest a primary gonadal problem, whereas a hypothalamic-pituitary disorder is likely if both LH and testosterone are low. Because TSH is a sensitive indicator of thyroid function, it is generally recommended as a first-line test for thyroid disorders.

- An elevated TSH level is almost always the result of primary hypothyroidism, whereas a low TSH is most often caused by thyrotoxicosis. These predictions can be confirmed by determining the free thyroxine level. Elevated calcium and PTH levels suggest hyperparathyroidism, whereas PTH is suppressed in hypercalcemia caused by malignancy or granulomatous diseases. A suppressed ACTH in the setting of hypercortisolemia, or increased urine free cortisol, is seen with hyperfunctioning adrenal adenomas.

- It is not uncommon, however, for baseline hormone levels associated with pathologic endocrine conditions to overlap with the normal range. In this circumstance, dynamic testing is useful to further separate the two groups. There are a multitude of dynamic endocrine tests, but all are based on principles of feedback regulation, and most responses can be remembered based on the pathways that govern endocrine axes.

- *Suppression tests* are used in the setting of suspected endocrine hyperfunction. An example is the dexamethasone suppression test used to evaluate Cushing's syndrome . *Stimulation tests* are generally used to assess endocrine hypofunction. The ACTH stimulation test, for example, is used to assess the adrenal gland response in patients with suspected adrenal insufficiency. Other stimulation tests use hypothalamic-releasing factors such as TRH, GnRH, CRH, and GHRH to evaluate pituitary hormone reserve .

- Insulin-induced hypoglycemia evokes pituitary ACTH and GH responses. Stimulation tests based on reduction or inhibition of endogenous hormones are now used infrequently. Examples include metyrapone inhibition of cortisol synthesis and clomiphene inhibition of estrogen feedback.

- Screening and Assessment of Common Endocrine Disorders
- Many endocrine disorders are prevalent in the adult population, and can be diagnosed and managed by general internists, family practitioners, or other primary health care providers. The high prevalence and clinical impact of certain endocrine diseases justifies vigilance for features of these disorders during routine physical examinations; laboratory screening is indicated in selected high-risk populations.