

**1- What are trophic hormones?**

- Hormones secreted by the anterior pituitary, which influence hormone secretion by other endocrine glands such as thyroid, adrenal cortex, etc., are termed *trophic hormones*.
- The trophic hormones are, in turn, controlled by the hypothalamus which synthesizes regulatory peptides that are transported by the hypothalamic portal system to the anterior pituitary.

**2- Enumerate the factors that regulate secretion of anterior pituitary hormones.**

The factors regulating anterior pituitary hormone secretion include the following:

- Stress (physical, mental, emotional or hypoglycemia).
- Increased plasma levels of target cell hormones, which exert feedback inhibition.
- Circadian rhythm: This may be lost in disease states.
- Drugs: For example, L-dopa stimulates GH secretion.

**3- Give a brief account of the anterior pituitary hormones.**

1. *Growth hormone (GH)* regulates growth and intermediary metabolism. GH secretion is stimulated by growth hormone releasing hormone (GHRH), and inhibited by *growth hormone release inhibiting hormone (GHRH)* or somatostatin.
2. *Thyroid-stimulating hormone (TSH)* regulates thyroid function. TSH secretion is stimulated by *thyrotropin releasing hormone (TRH)*.
3. *Adrenocorticotrophic hormone (ACTH)* stimulates glucocorticoid synthesis, and secretion from the adrenal cortex. It is regulated by *corticotrophin-releasing hormone (CRH)* from the hypothalamus.
4. *Luteinizing hormone (LH)* plays a role in ovulation, progesterone synthesis, and testosterone production. It is under the control of hypothalamic *gonadotrophin-releasing hormone (GnRH)*.
5. *Follicle-stimulating hormone (FSH)* regulates estrogen synthesis, oogenesis, and spermatogenesis. It is regulated by GnRH.
6. *Prolactin* acts on the mammary gland to induce lactation. It is regulated by *prolactin-release inhibiting hormone (PRIH)*, and TSH.
7.  *$\beta$ -Lipotrophin* is a neurotransmitter and endorphin precursor that is regulated by CRH.

**4- Give an account of the secretion and biological effects of growth hormone.****ⓐ Secretion**

- Growth hormone (GH) or *somatotrophin* is secreted by somatotrophs in the anterior pituitary.
- The human GH (hGH) is a single polypeptide chain containing 191 amino acid residues.
- Binding of GH to its receptor causes dimerization and phosphorylation of the receptor with activation of JAK2 tyrosine kinase and other signaling pathways.
- GH secretion
  - is low in infancy.
  - increases during early childhood.
  - reaches peak levels at puberty.
  - decreases after the third decade
- Plasma GH is episodic and pulsatile, and shows diurnal variations with peak values seen during sleep.
- Stimuli for GH secretion include:
  - stress
  - hypoglycemia
  - fasting
  - glucagon
  - exercise, arginine
  - drugs such as L-dopa
- GH secretion is inhibited by hyperglycemia.

**ⓐ Biological effects**

- *Growth promotion* by inducing hepatic synthesis of *insulin-like growth factors (IGF) or somatomedins*.
- *Carbohydrate metabolism* that
  - Increases blood glucose levels by increasing hepatic glucose production and decreasing peripheral utilization.
  - Inhibits glucose transport and glycolysis.
- *Lipid metabolism* that mobilizes adipose tissue fat with increase in plasma free fatty acids which inhibit insulin release from the pancreas.
- *Protein metabolism* that
  - increases protein synthesis by stimulating amino acid uptake

- increases amino acid transport into muscle.
- *Other effects*
  - retention of Na<sup>+</sup>, K<sup>+</sup>, and Cl<sup>-</sup>
  - prolactin-like effects such as lactogenesis.
  - stimulation of bone growth by promoting a positive calcium, phosphate, and magnesium balance.
  - increase cartilage formation.

### 5- How is the secretion of growth hormone regulated?

- GH secretion is
  - Stimulated by *growth hormone-releasing hormone (GHRH)* in a process that is calcium-dependant and mediated by cAMP, and
  - Inhibited by *growth hormone-release inhibiting hormone (GHRH)* or somatostatin.

Somatostatin synthesized by the hypothalamus, gastrointestinal tract, and the D cells of the pancreatic islets decreases the response of GH to secretagogues.

- GH release is influenced by various factors that act via GHRH and/or somatostatin.
  - IGF-I inhibits GHRH release and stimulates somatostatin secretion. An increase in IGF-I/SM- C leads to inhibition of GH secretion and a decrease releases GH.
  - The neurotransmitter dopamine stimulates GHRH secretion, whereas acetylcholine and gamma- aminobutyric acid (GABA) inhibit somatostatin.
  - $\alpha$ -Adrenergic blockers such as phentolamine inhibit GH release, while ( $\beta$ -adrenergic blockers stimulate GH secretion by inhibiting somatostatin secretion.
  - Thyroid hormones, VIP, cAMP, Ca<sup>+2</sup>, and Na<sup>+</sup> inhibit GH secretion by increasing somatostatin release.

### 6- Discuss the clinical features, diagnosis of growth hormone excess.

Excess growth hormone secretion causes gigantism in children and acromegaly in adults,

**AT** *Gigantism*

- Occurs in childhood before fusion of the epiphyseal plates.
- Affected children' may reach a height of 7 - 9 feet.
- Is characterized by postural defects.
- Results in death due to infection, cardiac failure, or pituitary tumor.

**AT** *Acromegaly*

- Occurs after epiphyseal fusion in middle age.

**AT** *Clinical features*

- Overgrowth of bone and soft tissue.
- Enlargement of hands, jaw, heart, tongue, larynx, liver, and kidney.
- Protruding jaw and enlarged nose.
- Excessive sebaceous gland secretion with oily skin.
- Increase in BMR with increased sweating.
- Headache, and muscle weakness.
- Hypertension associated with low renin and aldosterone secretion.
- Hirsutism and amenorrhea in women.
- Impaired glucose tolerance and diabetes mellitus.
- Death due to cardiovascular, cerebrovascular and respiratory diseases or malignancy.

**AT** *Diagnosis*

- Measurement of plasma GH
- *Glucose-suppression test*: An increase in plasma GH level riot1 suppressed by high plasma glucose suggests autonomous GH secretion.

The test involves oral administration of glucose (75 g in 300 mL) and estimation of plasma glucose and GH before the glucose load and at 30, 60, 90, and 120 minutes after glucose intake. In normal subjects, glucose suppresses plasma GH concentration, whereas in acromegaly, there is failure of suppression.

- Increased serum IGF-I concentrations.

**7- Elucidate the different types of dwarfism due to GH deficiency.**

Ⓐ *GH deficiency causes dwarfism in children.*

Three major types of dwarfism occur due to GH deficiency. They differ in the response to GH stimulation and plasma GH levels, as detailed below:

1. *GH-deficient dwarfs*

- have low levels of plasma IGF-I and IGF-II
- show normal response to GH administration.

2. *Pygmies*

- have normal plasma levels of GH and IGF-II
- have low levels of plasma IGF-I
- the underlying cause may be a post-GH receptor defect.

3. *Laron type dwarfs*

- have high plasma GH
- have low plasma IGF-I and IGF-II levels
- lack functional GH receptors.

Ⓐ *Diagnosis*

Low plasma GH during sleep and after exercise. Insulin stimulation test is performed to rule out GH deficiency. The test involves administration of insulin (0.15 U/kg body weight) to induce hypoglycemia. Blood samples are withdrawn before injection and at 30,60,90, and 120 minutes after the injection. Plasma GH level should be greater than 20 mU/L.

**8- Elucidate the synthesis and regulation of ACTH secretion.**

Ⓐ *Synthesis*

- ACTH is a single polypeptide containing 39 amino acid residues. It is synthesized by corticotrophs of the anterior pituitary as a large precursor molecule called *pro-opiomelanocortin (POMC)* of 285 amino acids.
- Cleavage of POMC yields ACTH and  $\beta$ -lipotrophin.

Ⓐ *Regulation*

- The release of ACTH is pulsatile and exhibits diurnal variations, with peak levels at 0800 hours and lowest levels at midnight.
- ACTH release is regulated by hypothalamic *corticotrophin releasing hormone (CRH)*, which increases POMC mRNA in a cAMP-dependent process.

- ACTH secretion is stimulated by:
  - Stress due to surgery and hypoglycemia by increasing CRH release, and
  - Immune mediators such as interleukins.
- ACTH secretion is inhibited by Cortisol, which inhibits CRH secretion.

### 9- Enumerate the biological effects of ACTH.

Ⓐ ACTH binds to specific receptors on the plasma membrane of adrenal cortical cells, increases cAMP levels, and

- Promotes synthesis and secretion of adrenal cortical steroids by stimulating the conversion of cholesterol to pregnenolone
- Regulates Cortisol secretion from the adrenal cortex and influences aldosterone secretion
- Maintains the size and integrity of the adrenal cortex.

Ⓐ The biological effects of ACTH mediated via the adrenal cortical steroids include the following:

- Increased gluconeogenesis
- Increased adipose tissue lipolysis
- Increased ketogenesis
- Decreased protein synthesis (except in the liver)
- Stimulation of salt and water reabsorption by the kidney.

Ⓐ Acting independently, ACTH exerts the following actions in tissues other than the adrenal cortex:

- Pigmentation due to its melanocyte-stimulating hormone (MSH) activity
- Glucose utilization and fatty acid release by the adipose tissue in vitro
- Activation of triglyceride lipase in adipose tissue by cAMP stimulation
- Stimulation of insulin release from pancreatic islet cells.

### 10- What is Kallman's syndrome?

Kallman's syndrome refers to congenital isolated gonadotropin deficiency that occurs in postmenopausal women and in men with primary hypogonadism. LH and FSH levels are reduced due to defective synthesis or release of GnRH. Clinical symptoms

include skeletal defects, mental retardation, cryptorchidism, and anosmia (lacking the sense of smell).

### 11- Describe the secretion, biological effects, and regulation of prolactin.

#### ⓐ *Synthesis and secretion*

- *Prolactin (PRL, lactogenic hormone, mammatrophin, luteotrophic hormone)*, synthesized by lactotrophs of the anterior pituitary, is a single polypeptide with 198 amino acid residues and three intrachain disulphide bonds,
- Prolactin secretion
  - is high during sleep and stress
  - is higher in women than in men.
- High estrogen levels during pregnancy increase prolactin secretion from the pituitary and inhibit secretion in the breast.
- Low estrogen levels postpartum lead to commencement of lactation,
- After delivery, there is a rapid fall in prolactin levels.

#### ⓐ *Biological effects*

- Initiation and maintenance of lactation,
- Weak GH-like effects such as
  - lipid mobilization
  - anabolic effects
  - anti-insulin action,
- Inhibition of the effects of gonadotrophins on ovarian steroidogenesis.
- *Prolactin receptors* are present in the plasma membrane of mammary gland, gonads, liver, and adrenal glands.
- Hormone - receptor interaction increases synthesis of milk proteins such as casein.
- Prolactin receptor concentration is increased by :
  - prolactin (an exception to the phenomenon of downregulation of receptors by hormones),
  - glucocorticoids
  - thyroid hormones.
- Prolactin receptor concentration is decreased by progesterone.

**AT** Regulation

- Prolactin secretion is inhibited by :
  - Dopamine from the hypothalamus by lowering cAMP levels. Increased plasma prolactin level, feedback inhibit hormone synthesis by enhancing dopamine synthesis.
  - *GnRH-associated peptide (GAP)*, a neuropeptide that has both GnRH and *prolactin-release inhibiting hormone (PRIH)* activities.
- Prolactin secretion is stimulated by :
  - TRH from the hypothalamus
  - Vasoactive intestinal peptide (VIP) during lactation.

**12- What are the hormones secreted by the posterior pituitary?****AT** The posterior pituitary secretes

- *Oxytocin*, which regulates lactation and stimulates uterine contraction.
- *Vasopressin or antidiuretic hormone (ADH)*, which stimulates water reabsorption from the renal B tubules and collecting ducts.

Both the hormones are synthesized in the hypothalamus and transported together with the corresponding carrier proteins neurophysins I and II to the posterior pituitary gland.

**13- Enumerate the biological actions of vasopressin.****AT** Vasopressin

- Increases blood pressure and peripheral vasoconstriction (in pharmacological amounts) mediated by the following sequence of events:
  - I. binding of vasopressin to the V1 receptors
  - II. activation of phospholipase C
  - III. generation of inositol triphosphate (IP3) and diacylglycerol
  - IV. increase in intracellular  $\text{Ca}^{+2}$
  - V. activation of protein kinase C
- Stimulates reabsorption of water from the renal distal convoluted tubules (DCT) and collecting ducts by promoting permeability of these cells to water and concentrating the urine. This is mediated by the following sequence of events:

- I. binding of vasopressin to the V2 receptor
- II. activation of adenylate cyclase by the hormone - receptor complex
- III. generation of cAMP
- IV. activation of a membrane-bound protein kinase by cAMP
- V. phosphorylation of membrane proteins
- VI. increased permeability to water.

#### 14- Discuss the causes, diagnosis of diabetes insipidus.

Ⓐ *Diabetes insipidus is characterized by*

- Excretion of excessive amount of urine (*polyuria*).
- Compensatory excessive water intake (*polydipsia*) in response to thirst.
- Diluted urine with urine volume ranging between 2.5 and 6 L/d in mild cases, and between 16 -24 L/d in severe cases.
- Increased plasma osmolality that stimulates thirst. If water is available, dehydration does not occur; whereas inadequate water intake can lead to severe dehydration with weakness, fewer mental disturbances, prostration, and death.

Ⓐ *Causes*

Diabetes insipidus may be of two types:

- *Central diabetes insipidus (cranial or neurogenic diabetes insipidus)* due to pituitary or hypothalamic disease results from the following causes:
  - I. Tumors and infiltrative lesions of the pituitary or hypothalamus such as pituitary adenomas craniopharyngiomas, sarcoidosis, etc.
  - II. Surgery of the pituitary or hypothalamus.
  - III. Severe head injuries such as fractures of the skull.
  - IV. Idiopathic, with circulating antibodies to hypothalamic nuclei,
- *Nephrogenic diabetes insipidus* in which vasopressin secretion is normal but the kidneys fail in respond to the hormone due to :
  - I. Congenital nephrogenic diabetes insipidus, resulting from V2 receptor abnormality.
  - II. Chronic renal diseases.
  - III. Potassium deficiency as in primary aldosteronism.
  - IV. Chronic hypercalcemia as in hyperparathyroidism.

- V. Systemic disorders such as multiple myeloma, sickle cell anemia, and sarcoidosis.
- VI. Pharmacological agents such as lithium.

Ⓐ *Diagnosis*

- Determination of plasma and urine osmolality.
- Fluid deprivation test to confirm diagnosis.

Ⓐ *Procedure*

The night before the test, fluids are allowed.

- i. A light breakfast without fluid is given the next morning.
- ii. The body weight is recorded and fluid withheld for 8 hours.
- iii. The weight of the patient is taken every one hour and the test stopped if the body weight falls by >3%.
- iv. After 8 hours, the patient is allowed fluid.
- v. Desmopressin (1-desamino-D-arginine-vasopressin) is administered subcutaneously (1 ug) or intranasally (10 ug).
- vi. Urine samples are collected every one hour for 4 hours.

Ⓐ *Interpretation*

In normal subjects, deprivation of fluid concentrates the urine and plasma osmolality does not exceed 295 mmol/kg. In diabetes insipidus, there is impairment of the concentration mechanism and plasma osmolality exceeds 300 mmol/kg. Following desmopressin injection, the urine becomes concentrated in patients with cranial diabetes insipidus, but remains dilute in nephrogenic diabetes insipidus.

## 15- Outline the diagnostic tests of SIADH.

Ⓐ *Diagnosis*

1. Concentrated urine with osmolality >300 mmol/kg.
2. Plasma osmolality <270 mmol/kg.
3. Low blood urea nitrogen (BUN), serum urate, creatinine, and albumin.
4. Plasma sodium <130 mmol/L.

5. Water load test to be carried out only when plasma sodium levels are  $>125$  mmol/L.

The test involves administration of 20 mL water/kg body weight up to 1500 mL and collection of one-hourly urine samples.

**Normal response:** At least 65% of the water is excreted in 4 h and 80% in 5 h with the lowest urinary osmolality ( $<100$  mmol/kg) seen in the second hour. In SIADH, and in adrenal and renal insufficiency, there is an inability to excrete the water load.

### 16- Enumerate the biological actions of oxytocin.

Oxytocin, a nanopeptide with cysteine residues at positions 1 and 6 linked by a disulphide bond, close structural homology with vasopressin.

#### Ⓐ Biological actions

- Contraction of the uterine smooth muscle in pharmacological amounts. The hormone is clinically used to induce labour.
- Promotion of milk ejection on suckling (milk letdown response).
- Stimulation of the contraction of myoepithelial cells surrounding the mammary alveoli causing milk release.
- Mild antidiuretic effects.
- Increased glucose oxidation and glucose utilization by adipose tissue at high concentrations.

#### Ⓐ Oxytocin receptors

- These are present on the membrane of uterine and mammary cells
- Their number is increased by estrogens, and decreased by progesterone.

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