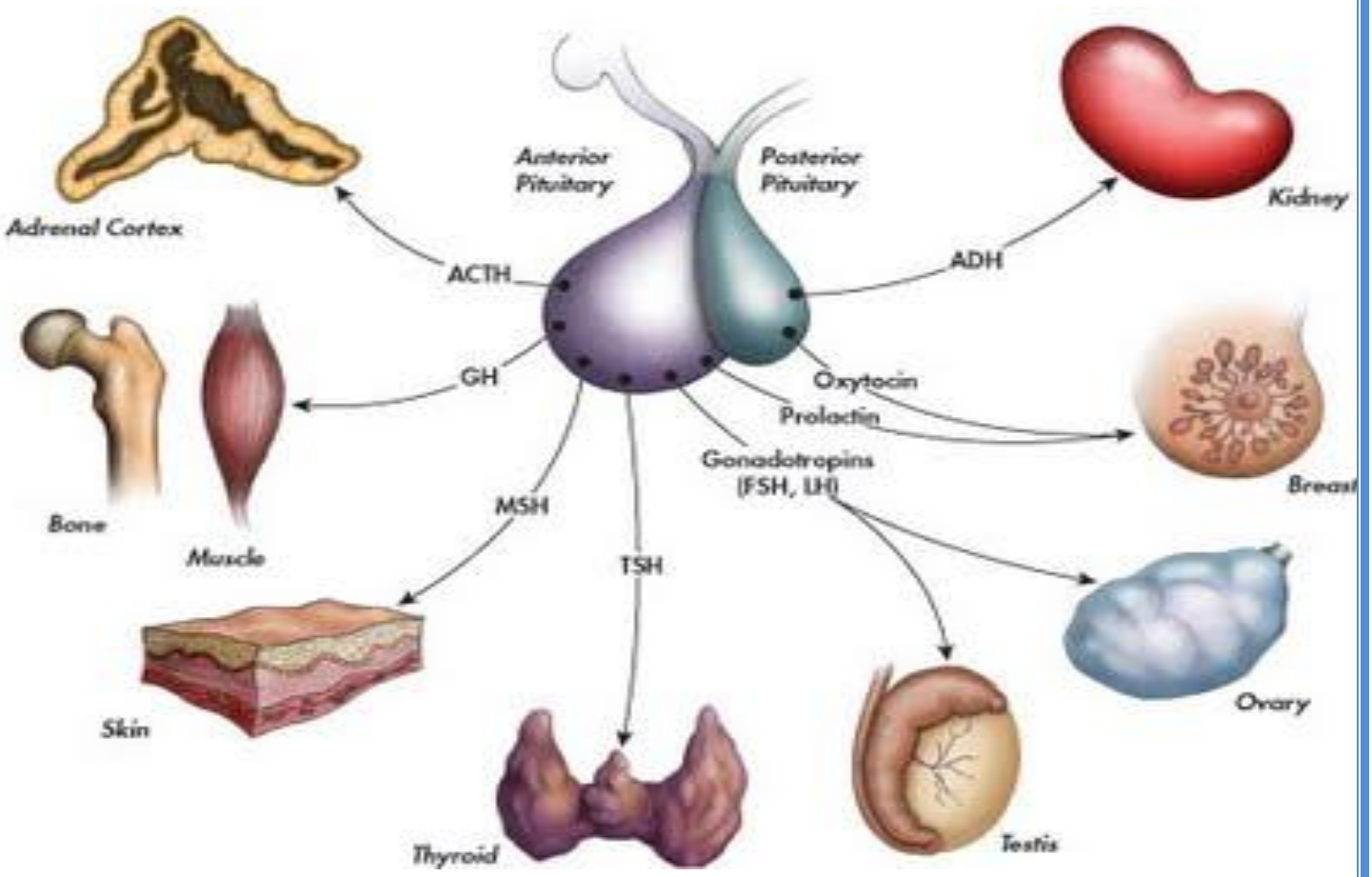
Endocrine Block

Physiology Team Summary



Physiology Team – 430

Physiology Team Leaders:

Al-Waleed Al-Johar

Layan Akkielah

Physiology Team Members

Faisal Al-Thunayan

Ali Al-Qahtani

Sulaiman Al-Faraj

Ahmed Bogari

Sara Al-Hilali

Hanan Al-Amer

Sara Al-Sukait

Hadeel Al-Sajjan

Hanan Al-Shalan

Shahad Al-Muhanna

Yara Al-Saif

Organized by : Al-Waleed Al-Johar

Introduction to the Endocrine system

- **Definition of Hormone:**

  Hormone is a chemical substance released in a small amount by group of cells directly to the blood stream in response to stimulus to cause physiological response at the target tissues

- **Chemical classification of hormones:**

1) **Proteins and Polypeptides:** From amino acids and they are stored (e.g. insulin, parathyroid hormone, and pituitary hormones)
2) **Steriods:** From cholesterol and they diffuse cell membrane (e.g. cortisol, estrogen and aldosterone)
3) **Amines:** From tyrosine (e.g. Thyroxine, T_3)

- **Classification of stimuli:**

1. **Humoral stimuli:** secretion of hormones in direct response to changing in blood levels of ions and nutrients.
2. **Neural stimuli:** nerve fibers stimulate hormone release
3. **Hormonal stimuli:** release of hormones in response to hormones produced by other endocrine glands

- **Transport of hormones:**

1. **Water Soluble**
2. **Lipid soluble**

- **Regulation of hormone secretion:**

1. **Neural mechanism:**

   Direct stimulation of secretion by the nervous system

2. **Feedback mechanism:**

- Negative feedback mechanism: if the hormone concentration in blood was high, the gland will stop the secretion of that hormone
- Positive feedback mechanism: it is uncommon, and it means that the hormone can stimulate its gland to secret more of itself (e.g. oxytocin)

✓ **Autocrines:** chemicals that exert their effects on the same cells that secrete them
✓ **Paracrines:** locally acting chemicals that affect cells other than those that secrete them

- **Mechanism of hormone action:**

- **Protein hormones:**

✓ Adenylyl cyclase system

✓ Phospholipase C system

✓ Tyrosine kinase system

- **Steroid hormones:**

✓ Act on the genetic machinery of the cell

- **Target tissue:**

- Hormone (1st messenger)-receptor interaction → Enzyme activation → Release of the second messenger → Effects on cellular function

- **Receptor's Location:**

1) On the surface of cell membrane (proteins, peptides and catecholamine hormones)
2) In the cell cytoplasm (Steroids)
3) In the cell nucleus (thyroid hormones)

✓ **Hydrophilic hormones:** can't enter the cell→ hence; they only bind on an outer surface receptor→ resulting in a fast response

✓ **Lipophilic hormones:** (steroid and thyroid) can enter the cell→ often lead to gene activation→ Therefore, they result in a slower response

- **Regulation of hormone receptors:**

1) **Dose-response relationship:**
2) **Sensitivity:**
3) **Number and affinity:**

- **Down-regulation:**

✓ Decrease synthesis - Increase degradation – Inactivation - E.g.: T3, progesterone

- **Up-regulation:**

✓ Increase synthesis - Decrease degradation – activation - Estrogen, GH, prolactin

- **Interactions of hormones at target cells:**

1) **Synergism:** It occurs when more than one hormone produces the same effects
   E.g.: glucagon, cortisol and epinephrine
2) **Permissiveness:** One hormone allows another hormone to have its full effect
   It occurs especially during growth and development
   E.g.: Thyroid hormone has permissive effect on growth hormone action
3) **Antagonism:**
   It means that one hormone decreases the action of the other
   E.g.: Glucagon /insulin

Hypothalamic-Pituitary Axis

1- GHRH and GHIH/Somatostatin:

✓ **Growth hormone releasing hormone (GHRH)**

- Stimulates release of growth hormone

✓ **Growth hormone inhibiting hormone (GHIH) also called Somatostatin**

- Inhibits release of growth hormone

2- Thyro-tropin releasing hormone:

- Stimulates release of thyroid stimulating hormone (TSH)

3- Corticotropin-Releasing hormone:

- Stimulates release of adrenocorticotropin hormone (ACTH)

4- Gonadotropin Releasing hormone:

- It causes release of the 2 gonadotropic hormones:

1. Luteinizing (**LH)**
2. Follicle-stimulating hormone **FSH**

5- Prolactin inhibitory hormone:

- Also known as: Dopamine
- Inhibits prolactin secretion

- **Relationship of the Hypothalamus to the anterior pituitary:**

- The anterior lobe is primarily a collection of endocrine cells.
- The anterior pituitary secretes 6 peptide hormones, From 5 different cell types: Somatotrops (GH) – Thyrotrops (TSH) – Corticotrops (ACTH) – Lactotrops (PRL) Gonadotrops (LH &FSH)
- Connected to each other by Hypothalmaic-Hypophyseal portal vessels

- **Relationship of the Hypothalamus to the posterior pituitary:**

- The posterior lobe of pituitary is collection of nerve axons and supporting cells.
- It secretes 2 peptide hormones: ADH (Supraoptic Nuclei) and oxytocin (Paraventricular Nuclei)
- The connections between the hypothalamus and the posterior lobe of pituitary gland are neural (hypothalamo-hypophyseal tract)

- **Negative feedback loop reflexes:**

- **Long-loop feedback** → means that the hormone feeds back all the way to the hypothalamic-pituitary axis.
- **Short-loop feedback** → means that the anterior hormone feeds back on the hypothalamus to inhibit secretion of hypothalamic-releasing hormone

Anterior Pituitary gland (adenohypophysis)

1) Growth Hormone (somatotropin)

Growth hormone (GH) stimulates body cells to **increase in size and divide**

- **Regulation of GH**:

- **Stimulation:** GHRH - Muscular exercise - Intake of protein or amino acids – Hypoglycemia – Ghrelin – sleep - Stress conditions
- **Inhibition:** GHIH – somatostatin – FFAs - Negative feedback - glucose intake

- **Mechanism of action:**

– **Direct effect :**

The action of GH on its receptors which are located on the target tissue

– **Indirect effect :**

The Liver produces and secretes somatomedins (insulin –like growth factors) in response to GH stimulation

- **Functions of GH:**

A) Long term effect : Promotion of growth (due to the indirect effect) :

↑ cellular sizes & ↑ mitosis &↑ tissue growth & organ size

B) Short term: Metabolic effects:

– **Effects of GH on Protein metabolism (Anabolic) :**

➢ rate of protein synthesis in all cells through:

✓ amino acids transport into cells (increase amino acid concentration in cell → increase protein synthesis)

✓ ↑DNA transcription → RNA synthesis → protein synthesis

✓ ↑RNA translation → protein synthesis

✓ ↓protein catabolism "protein sparer"

– **Effects of GH on Fat metabolism: Catabolic :**

✓ ↑Mobilization of FFAs from adipose tissue stores.

✓ Conversion of FFT to acetyl CoA to provide energy.

– **Effects of GH on CHO metabolism: Hyperglycemic:**

✓ ↓ Glucose uptake by tissues (skeletal muscles and fat).

✓ ↓ Rate of glucose utilization throughout the body.

✓ ↑ Glucose production by the liver (↑ gluconeogenesis).

These changes are due to ↑ insulin resistance (↑FFA) (diabetogenic)

- **Abnormalities of GH :**

- **Hyposecretion** of GH in childhood → Dwarfism
- **Hypersecretion** of GH in childhood → Gigantism
- **Hypersecretion** of GH in adults → Acromegaly

2) Prolactin :

Secreted in both males and females & Related to GH

- **Regulation of Prolactin :**

- **Stimulation:** Pregnancy – Lactating – TRH – Dopamine antagonist
- **Inhibition:** Dopamine – Bromocriptine – Somatostatin – Negative Feedback

- **Functions of PRL :**

– Stimulation of milk production
– Effect on the breast :
Increases mRNA, Increases production of casein, Inhibits the effects of gonadotropins
– Stimulates the secretion of dopamine in median eminence

- **Sources of Dopamine:**

1. Dopaminergic neurons in the hypothalamus.
2. Dopaminergic neurons in the posterior pituitary.
3. Nonlactotrophs cells of the anterior pituitary.

- **Abnormalities:**

1- **PRL deficiency:** failure to lactate
2- **PRL Excess:** Galactorrhea, Infertility

3) FSH & LH :

Related to TSH

- **Secretion :**

In male: they help in secreting Testosterone
In female: they help in secretion of Progesterone & Estrogen

4) ACTH:

- **Formation :**

To form this hormone, it requires a precursor named Preproopiomelanocortin (POMC), due to the cleavage of this precursor, it will produce along with the ACTH other hormones, they are: Melanocyte Stimulating hormone and β-endorphin

- **Regulation of ACTH :**

- **Stimulation:** ↓ Cortisol – ADH - Serotonin – β-Adrenergic antagonist – α-Adrenergic agonist – Stress
- **Inhibition:** ↑ Cortisol – Opioids – Somatostatins

Posterior pituitary gland (neurohypophysis)

1. ADH (Anti-diuretic hormone):

- It is a polypeptide formed from nine amino acids.
- Synthesized in the supraoptic nuclei

• Mechanism of action of ADH :

- ADH in kidneys → ↑ Water absorption
- ADH binds to V_2 → Adnylyl Cyclase → cAMP → Aquaporins → Water diffusion

• Regulation of ADH secretion :

- **Osmotic regulation:**

✓ ADH secretion is very sensitive to changes in osmolality.
✓ ↑ Osmolality → ↑ ADH via osmoreceptors

- **Non- osmotic regulation:**

✓ Hypovolemia causes increase in ADH secretion by Pressure receptors
✓ Normally, pressure receptors tonically inhibit ADH release

- **Stimuli that increase ADH secretion:** Pain, Nausea, Surgical stress, Emotional stress
- **Stimuli that decrease ADH secretion:** Alcohol intake

2. Oxytocin:

1) Milk ejection:

- Targets the female breast of lactating women to release milk
- Note that milk formation is by the hormone Prolactin , but milk release (when the infant suckles the mother) is by Oxytocin
- Then oxytocin acts on myoepthelial cells → contraction → expression of milk from its site of synthesis into larger ducts of the breast → milk excretion

2) Uterine Contraction:

- Stimulation of mechanoreceptors in the uterine cervix and vagina during labor (parturition) cause a rise in oxytocin levels → uterine contraction
- This helps in:

1) Expulsion of the baby during labor
2) Stopping bleeding after delivery
3) Also, after the baby is born & as the mother breastfeeds him → baby suckling produces oxytocin release → milk let-down + uterine contraction (which prevents further blood-loss from the mother)

• Regulation:

– Regulated by higher brain centers and positive feedback
– Release increased during stress & inhibited by alcohol

Diabetes Insipidus

- **Diabetes insipidus (DI) is a condition where the person:**

- Polyuria - Feels thirsty - polydipsia

- **Polydipsia:**

It differs from diabetes mellitus in that

- Urine is dilute - no glycosuria - Blood sugar is normal - Reduction of fluid intake does not change urine concentration

- **Types of Diabetes Insipidus:**

Mainly 2 types:

- **Cranial DI (The commonest):** due to vasopressin (ADH) deficiency → defect in the posterior pituitary gland. (The defect can also be in the Hypothalamus or Pituitary stalk)
- **Nephrogenic DI:** there is enough ADH is being but the kidney fails to respond to it → defect in the kidney.

- **Other conditions that also manifest polydipsia and should not be confused with DI are:**

- Psychogenic Polydipsia (Physiological ADH inhibition)
- Diabetes mellitus

- **Signs of hypovlemia (decreased ECF volume) & dehydration such as:**

- Poor skin turgor & dryness of the skin & mucous membranes
- Small (weak), tachycardia, & hypotension
- Haemoconcentartion & increased plasma osmolarity
- Increased body temperature & hyperthermia if treatment is delayed
- If we decrease the patient's water intake, his urine output does not decrease → this proves that the patient cannot produce ADH in response to decreased ECF volume
- If left untreated, diabetes insipidus can result in severe dehydration, shock and death

- **Management**

- Strict measurement & recording of fluid intake & urine output + urine specific gravity & testing and osmolarity testing hourly in the early stages
- Recording the pulse and BP hourly in the early stages , to detect early any signs of shock
- Vasopressin test → If desired , Vasopressin can be injected subcutaneously → if urine output decreases → this is not nephrogenic DI
- Pitressin (aqueous vasopressin) can be used for treatment

- **Psychogenic Polydipsia :**

- In this condition the person has psychologic urge (strong desire) to drink much water though he doesn't need it .
- He has normal ADH l secretion & normal kidney response to ADH , but the patient has psychiatric disturbance that produces urges to drink large amounts of water .
- Urine has large volume & is dilute
- However, if you deprive this person of water → urine volume decreases & urine osmolarity increases (urine becomes more concentrated)
- Subject shows normal response to water restriction

Thyroid Gland

- **Thyroid Hormones:**

- T3 Triiodothyronine 10% → (more potent)
- T4 thyroxine (tetraiodothyronine) 90% → (more abundant)
- Reverse T3 (inactive)
- Calcitonin

- **Steps in Biosynthesis:**

1) Thyroglobulin Formation And Transport

2) Iodide Pump Or Iodide Trap

- Wolff-chaikoff effect (Increase amount of iodine in blood → decrease the activity of iodide pump vice versa)

3) Oxidation Of Iodide To Iodine

- It is catalyzed by Thyroid peroxidase which is located in or attached to the apical membrane
- Iodine is the reactive form, which will be "organified" by combination with tyrosin on thyroglobulin

4) Organification Of Thyroglobulin

- Binding of iodine with Thyroglobulin
- Catalyzed by thyroid peroxidase to form: monoiodotyrosine MIT - Diiodotyrosine DIT
- Remain attached to thyroglobulin until the gland stimulated to secret

5) Coupling Reaction:

- DIT + DIT = T4 (faster)
- DIT + MIT = T3
- Catalyzed by thyroid peroxidase

6) Endocytosis of thyroglobulin

7) Fusion of lysosomes immediately with the vesicles

8) Hydrolysis of the peptide bond to release DIT+MIT+T4+T3 from the thyroglobulin

9) Delivery of T4 and T3 to the systemic circulation.

10) Deiodination of DIT and MIT by thyroid deiodinase (Recycling)

- **Thyroid Hormones in the Circulation:**

1. **Bound:**

- 70- 80% bound to thyroxine-binding globulin (TBG) synthesized in the liver
- The reminder is bound to albumin

2. **Unbound (Free)**

✓ **In hepatic failure:**
↓ TBG → ↑ free T3/T4 → inhibition of thyroid secretion

✓ **In pregnancy:**
↑ Estrogen → ↑ TBG → ↓ free T3/T4 → stimulation of thyroid secretion

- **Release of T4 and T3 to the Tissues:**

- T4 & T3 readily diffuse through the cell membrane
- Stored in the targeted tissues (days to weeks)
- Most of T4 is deionized to T3 by iodinase enzyme
- In the nucleus, T3 mainly binds to "thyroid hormone receptor" and influence transcription of genes

1) Basal Metabolic Rate (BMR):

Complete lake of thyroid hormones → 40-50% ↓ in BMR
Extreme increase of thyroid hormones → 60-100% ↑ in BMR

2) Metabolism:

✓ **Effect on carbohydrate metabolism:**

- Increase glucose uptake by the cells, glycogenolysis, gluconeogenesis, and absorption from the GIT

✓ **Effects on fat metabolism:**

- Increase lipolysis, Decrease plasma cholesterol by increase loss in feces, and Increase oxidation of free fatty acids.

✓ **Effect on protein metabolism:**

- Overall effect is catabolic leading to decrease in muscle mass

3) Effects on the Cardiovascular system:

- Increase heart rate, stroke volume, Decrease peripheral resistance (These effects combine to produce increased cardiac output up to 60%)
- End result is increase delivery of oxygenated blood to the tissues

4) Effects on the CNS:

A. Peri-natal period:

- Decreased levels → Irreversible mental retardation

B. In adult:

✓ **Increase in thyroid hormone secretion:**

- Hyperexcitability, Irritability

✓ **Decrease in thyroid hormones secretion:**

- Slow movement, Impaired memory, ↓ Mental capacity

5) Effects on bone:

- Promote bone formation, ossification, fusion of bone plate, bone maturation

6) Effects on Respiration:

- Increase ventilation rate, dissociation of oxygen from Hb by increasing RBC 2,3-DPG (2,3 diphosphoglycerate)

7) Effects on the GIT:

- Increase appetite and food intake, digestive juices secretion, and motility

✓ Excess secretion → diarrhea

✓ Lake of secretion → constipation

8) Effects on Autonomic nervous system:

- Produced the same action as catecholamines via β-adrenergic receptors including:

✓ Increase BMR, heat production, heart rate, stroke volume
i.e. β-blocker (propranolol) is used in treatment of hyperthyroidism.

Table 9-8 Factors Affecting Thyroid Hormone Secretion

Stimulatory Factors	Inhibitory Factors
TSH	I^- deficiency
Thyroid-stimulating immunoglobulins	Deiodinase deficiency
Increased TBG levels (e.g., pregnancy)	Excessive I^- intake (Wolff-Chaikoff effect)
	Perchlorate; thiocyanate (inhibit Na^+-I^- cotransport)
	Propylthiouracil (inhibits peroxidase enzyme)
	Decreased TBG levels (e.g., liver disease)

Hyperthyroidism

- **Causes:**

1. **Graves' disease**
2. **Thyroid gland tumor**
3. **Exogenous T3 and T4**
4. **Excess TSH secretion:** **Di**seases of the hypothalamus (TRH) & pituitary (TSH).

- **Diagnosis:**

➢ **Based on the Signs and Symptoms:**

1. **Goiter in 95%** (increase in thyroid gland size)
2. **Skin:** Smooth, warm and moist, Heat intolerance, Night sweating.
3. **Musculoskeletal:** Muscle atrophy
4. **Neurological:** Tremor, Enhanced reflexes, Irritability
5. **Cardiovascular:** Increase heart rate & stroke volume, Arrhythmias, Hypertension.
6. **G.I tract:** Weight loss, Diarrhea.
7. **Renal function:** ↑ Glomerular filtration rate.
8. **Exophthalmos:** Anxious staring expression, Protrusion of eye balls.
9. **Others:** Menstrual cycle disturbance.

➢ **Based on the Investigations:**

	T3, T4	TSH
Primary Hyperthyrodism	High	Low
Secondary Hyperthyrodism	High	High

- **Treatment:**

1- **Medical therapy:** E.g. Propylthiouracil (Antithyroid agent)

2- **Surgery:**

- Subtotal thyroidectomy
- Indication for surgery: Relapse - Drug intolerance - Cosmetic - Suspected malignancy

Hypothyroidism

- **Causes:**

1. **Inherited abnormalities of thyroid hormone synthesis**
2. **Endemic Colloid Goiter**
3. **Idiopathic Nontoxic Colloid Goiter**
4. **Gland destruction (surgery)**
5. **Pituitary diseases or tumor**
6. **Hypothalamus diseases or tumor**

- **Diagnosis:**

➢ **Based on the Signs and Symptoms**

1. **Skin:** Dry Skin, Cold Intolerance
2. **Musculoskeletal:** ↑Muscle Bulk, ↓In Skeletal Growth, Muscle Sluggishness
3. **Neurological:** Slow Movement, Impaired Memory, Decrease Mental Capacity
4. **Cardiovascular:** ↓Heart rate, ↓Stroke volume
5. **G.I tract:** Constipation,Increase Weight
6. **Renal function:** ↓ Glomerular filtration rate
7. **Myxoedema:** An edematous appearance throughout the body
8. **Others:** Loss of libido, Menstrual cycle disturbance

➢ **Based on the Investigations**

	T3, T4	TSH
Primary Hypothyrodism	Low	High
Secondary Hypothyrodism	Low	Low

- **Treatment:** L-Thyroxine (Is a synthetic form of thyroid hormone)

Cretinism

- Extreme hypothyroidism during infancy and childhood (failure of growth)

- **Causes:**

1- Congenital lake of thyroid gland (congenital cretinism)
2- Genetic deficiency leading to failure to produce hormone
3- Iodine lake in the diet (endemic cretinism)

- **Symptoms:**

1- Infant is normal at birth but abnormality appears within weeks
2- Protruding tongue
3- Dwarf with short limbs
4- Mental retardation
5- Often umbilical hernia
6- Teeth

- **Treatment:**

- Changes are irreversible unless treatment is given early.