The Endocrine System

Specialist: Endocrinologist

Hormones

• A single hormone can initiate many different cellular responses in different cells

• Hormones released in one part of the body, travel through the blood and regulate activity of cells in another part of the body

• Some act within seconds, most within several minutes, some take hours or days to onset of action.

• Duration of action can be seconds to days

Strictly Endocrine Glands

• Pineal – Melatonin

• Pituitary – hGH, FSH, LH, TSH,

• Thyroid – T3, T4

• Parathyroid – PTH

• Adrenal – Aldosterone – Cortisol – Androgens – Epinephrine – Norepinephrine

Other Tissues/ organs that secrete hormones

• Some tissues or organs are not strictly endocrine glands and have other functions, in addition to secreting hormones.

• Hypothalamus

• Thymus

• Pancreas

• Ovaries

• Testes

• Kidneys

• Stomach

• Liver

• Small intestine

• Skin

• Heart

• Adipose

• Placenta
Endocrine Glands are highly vascularized

- Endocrine glands are very vascularized
- Gland cells secrete their products into the interstitial fluid
- The hormone then diffuses into the blood which carries it all over body
- Only cells with receptors for that hormone will react with an action

Chemical Classes of Hormones

**Lipid Soluble Hormones**: bind to receptors inside target cells

- Steroids
  - Aldosterone, cortisol, androgens – Adrenal cortex
  - Calcitriol - Kidneys
  - Testosterone - Testes
- Estrogen, Progesterone – Ovaries

- Thyroid
  - T3 (triiodothyronine)
  - T4 (thyroxine)

- Gases
  - Nitric Oxide

**Water Soluble Hormones**: bind to receptors on target cell surface

- Amines
  - Cocaine: epinephrine, norepinephrine, dopamine – adrenal medulla
  - Histamine – mast cells in CT
  - Serotonin – platelets

- Peptides & Proteins
  - Many, including: all hypothalamic releasing and inhibiting hormones; all pituitary hormones, such as oxytocin, ADH, FSH, LH, TSH, ACTH, HGH, MSH; insulin, glucagon, somatostatin,

- Eicosanoids
  - Eg Prostaglandins, Leukotrienes

Hormone Receptors

- **Lipid soluble** hormones, like steroids & thyroid hormone, affect cell function by entering the nucleus and directly altering gene expression

- **Water soluble** hormones activate plasma membrane receptors, which elicit *second messengers* that activate various enzymes inside the cells

Peptides, Amines, Steroids

- **Water soluble peptides or amines** bind to receptors on the surface of cells
- **Lipid soluble hormones** diffuse into the cell and bind receptors inside the cell
FYI - 2nd messengers: cAMP

- Water soluble hormones bind to surface receptors, & then activate a G protein.
- The G protein, then activates an enzyme, Adenylate Cyclase.
- Adenylate Cyclase catalyzes conversion of ATP into the 2nd messenger, cAMP (cyclic AMP)
- cAMP activates the enzyme, protein kinase, which can phosphorylate (add a phosphate) various proteins to activate them & produce a cellular action eg glycogen breakdown.

FYI - 2nd messengers: DAG & iP3

- Another example of a 2nd messenger.
- Activated G protein can then activate a different enzyme, Phospholipase C (PLC)
- PLC can activate both 2nd messengers, DAG & iP3...
- Binding of a single epinephrine molecule can activate 100 G proteins
- Each adenyl cyclate can produce 1000 cAMP...

Control of Hormone secretion

Hormone secretion is controlled by
- signals from the nervous system
- chemical changes in blood
- Other hormones
- Negative feedback

Hypothalamus

The main link between the nervous and endocrine system
Neurons in the hypothalamus are called Neurosecretory cells. These neurons of the hypothalamus secrete:
- Releasing Hormones, such as PRH (Prolactin Releasing Hormone), or TRH (Thyroid Releasing Hormone).
- Inhibiting Hormones, such as PIH (Prolactin Inhibiting Hormone).

Releasing and Inhibiting Hormones enter the Pituitary
- The hypothalamic neurons secrete their releasing and inhibiting hormones into a capillary network on the infundibulum, or pituitary stalk.
- The hormones then enter a second capillary network on the anterior pituitary via the hypophysial portal vein.
- Longer hypothalamic neurons reach the separate capillary network of the posterior pituitary directly.
- Releasing hormones exert their effects on the cells of the pituitary and cause them to release pituitary hormones into the blood.

Anterior Pituitary Hormones
Anterior pituitary endocrine cells produce the following anterior pituitary hormones:
- Somatotrophs produce Human Growth Hormone (hGH)
- Lactotrophs produce Prolactin (PRL)
- Corticotrophs secrete Adrenocorticotropic Hormone (ACTH) & Melanocyte Stimulating Hormone (MSH)
- Thyrotrophs secrete Thyroid-Stimulating Hormone (TSH)
- Gonadotrophs synthesize Follicle Stimulating Hormone (FSH) & Luteinizing Hormone (LH)

Posterior Pituitary: 1) ADH & 2) Oxytocin
- Hormones of the posterior pituitary are released directly from neurons that originate in the hypothalamus.
- The neurosecretory cells make Anti Diuretic Hormone (ADH) and Oxytocin. They release them into the blood from their axon terminals when stimulated to do so.
All Pituitary Hormones

Feedback Control of Pituitary Hormones
- The pituitary and hypothalamus have receptors for each of the hormones they stimulate production of.
- When blood levels of these hormones rise above a certain amount, the hypothalamus and pituitary will stop producing releasing hormones or pituitary hormones.
- This is called negative feedback.

INSULIN LIKE GROWTH FACTOR (IGF-1)

GROWTH HORMONE

Human Growth Hormone & Insulin Like Growth Factor
- hGH is most plentiful anterior pituitary hormone.
- When the pituitary secretes hGH, it stimulates the liver and other tissues to synthesize and secrete the protein hormone, IGF, insulin-like growth factor.
- IGF is also called somatomedin.
**IGF**

- **Stimulates growth** by increasing uptake of amino acids and speeding up protein synthesis. It decreases breakdown of proteins into amino acids for ATP production.

- **Enhances lipolysis**, using FA for ATP synthesis.

- **Raises blood sugar** by stimulating liver to make glucose

**EFFECTS**

- In children, promotes growth of skeleton and skeletal muscles

- In adults maintains muscle and bone mass, promotes tissue healing and repair

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**HYPOglycemia stimulates GHRH**

- Low glucose (hypoglycemia) stimulates the hypothalamus to release GHRH

- GHRH stimulates the pituitary to secrete hGH

- hGH stimulates the liver and other tissues to release of IGF

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**HYPERglycemia stimulates GHRIH**

- High IGF-1 or high blood glucose, stimulates the hypothalamus to secrete Growth Hormone Release Inhibiting Hormone (GHRIH), also known as somatostatin (SRIF)

- GHRIH inhibits pituitary secretion of hGH

- Low IGF slows glycogen breakdown in the liver & glucose enters the bloodstream more slowly

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**THYROID**

- TRH, THS, T3, T4
Thyroid Follicles

• The thyroid is located below the cricoid cartilage of the larynx

• It is made up of spherical sacs called thyroid follicles

• Follicular cells surround a lumen filled with sticky fluid colloid, made of thyroglobulin and iodine

• Parafollicular cells or C cells produce calcitonin

Synthesis of T4 & T3, Iodide & TGB

1. Follicular cells do the following:
   1. Actively trap iodide ions from the blood into the cytosol
   2. Synthesize Thyroglobulin (TGB). Adds tyrosine rings, and releases it into the lumen of the follicle
   3. The enzyme, Thyroid Peroxidase, TPO oxidizes iodide oxidized (removes an electron) to make it iodine and then couples it to tyrosine on thyroglobulin to create MIT, Moniodotyrosine, DIT, Diiodotyrosine, T3 & T4.

Coupling & Secretion of T3 & T4

• MIT or DIT will couple, joining to become T3 or T4
• Droplets of colloid re-enter the follicular cell by pinocytosis.
• Lysosomes break down thyroglobulin, cleaving off T3 & T4
• Lipid soluble T3 & T4 diffuse out of the follicular cell into blood

Transport protein: TBG

• >99% of T3&T4 combines with TBG, Thyroxine Binding Globulin, a transport protein that carries thyroid hormone in the blood
**T4 to T4 conversion**

- Most body cells have receptors for thyroid hormone
- T4 is converted to the more potent, T3 in the body tissues by deiodinase enzymes
- 60% of this conversion occurs in the liver

**Thyroid hormone targets & effects**

**EFFECTS OF T3:**

1. Increases Basal Metabolic Rate (ie rate of ATP synthesis by mitochondria)
   - Uses glucose and fatty acids for metabolism
   - Increases lipolysis and reduces cholesterol
   - Increases protein synthesis
2. Increases synthesis of Na/K/ATPase pumps
3. Upregulates beta receptors, thus increases effects of Epi & NE

**Thyroid Feedback inhibition**

- The hypothalamus and pituitary glands will detect elevated amounts of T3 and T4
- They will reduce production of TRH & TSH

**Thyroid detailed summary**
C cells/ parafollicular cells

- Elevated blood Ca\(^{2+}\) stimulates cells in between the follicles, called C cells or Parafollicular cells
- These cells secrete the hormone, calcitonin
- Calcitonin decreases Ca and Phosphates in the blood by inhibiting osteoclasts
- Accelerates uptake of Ca & Phosphate by bone

Parathyroid

- Decreased Ca\(^{2+}\) levels stimulate parathyroid chief cells to secrete PTH, parathyroid hormone
- This gland is a major regulator of Ca, Mg, HPO\(_4\)^{2-} (phosphate)
Parathyroid hormone functions

- PTH increases the activity of osteoclasts, which are involved in the breakdown and release of calcium, $\text{Ca}^{2+}$, and hydrogen phosphate, $\text{HPO}_4^{2-}$, from bone.

- PTH acts on the kidney to:
  - Increase the reabsorption of calcium, magnesium, and $\text{HPO}_4^{2-}$ into the blood.
  - Excrete $\text{HPO}_4^{2-}$ into the urine.
  - Make calcitriol, the active form of vitamin D.

- Vitamin D increases the absorption of calcium, magnesium, and $\text{HPO}_4^{2-}$ from the intestines.

Adrenal Cortex 80-90%

Adrenal Cortex has 3 zones:

- **Zona glomerulosa** secretes mineralocorticoids that affect mineral homeostasis, mainly **Aldosterone**.
- **Zona fasiculata** secretes glucocorticoids, which affect glucose homeostasis, mainly **Cortisol**.
- **Zona reticularis** secretes weak androgens, **DHEA**.

Mineralocorticoid: Aldosterone

- An increase in blood potassium, or Angiotensin II (from the renin-angiotensin-aldosterone system, RAA) makes the adrenal cortex release aldosterone.

  - Aldosterone causes:
    - Increased Na/K pumps causes:
      - Reabsorption of Na and water (if ADH is present)
      - Excretion of K+
    - Excretion of H+ prevents acidosis of the blood.
Glucocorticoid: Cortisol

Zona Fasiculata secretes
1. **Cortisol** (95%), also known as hydrocortisone
2. **Cortisone**
3. **Corticosterone**

- Low cortisol, stimulates the hypothalamus to secrete CRH.
- Any of the following can cause the pituitary to secrete ACTH
  - CRH
  - low glucose
  - physical trauma
  - stress
  - IL-1 from macrophages

Cortisol causes:
- **GLUCONEOGENESIS**, especially by the liver
  - Breakdown of muscle to liberate amino acids for making glucose
  - Fat breakdown. FA used for energy. Glycerol backbone used for gluconeogenesis
  - Inhibition of glucose uptake by muscle and adipose cells

Cortisol effects - Immune & stress

- Cortisol initiates many mechanisms to survive stressors such as trauma, blood loss, temp extremes, infection:
  - Raises blood sugar to make ATP, Depresses all immune responses
  - **Antiinflammatory** – inhibits WBCs to slow wound healing, which involves inflammation
  - Sensitizes blood vessels to vasoconstriction - Raises blood pressure (good if bleeding)

Androgens: DHEA

- DHEA is a weak androgen.
  - In children, DHEA contributes to the pre-pubertal growth spurt, growth of axillary and pubic hair
  - In males, such a small amount is secreted, so there are few effects
  - In females, it promotes libido, & is converted into estrogens by other tissues.
  - After menopause, **when ovarian secretion of estrogen ceases, all estrogen comes from conversion of adrenal androgens**
**Adrenal Medulla: Epi, NE**

- A modified sympathetic ganglion.
- Chromaffin cells of the adrenal medulla make 80% epinephrine (Epi) and 20% norepinephrine (NE).
- Under stress, the hypothalamus stimulates sympathetic preganglionic neurons that innervate chromaffin cells to secrete E, NE.
- **Flight or Fight** – increases HR, contractility, thus CO & BP. Increased blood to muscles & liver. Dilate airways, now can run!!

**Glucagon, Insulin, Somatostatin, Pancreatic Peptide**

**PANCREAS**

**Gluclagon & Insulin**

**Islets of Langerhans**

- α-cells (17%) secrete Glucagon
- β-cells (70%) secrete insulin
- δ-cells 7% secrete somatostatin
- F cells secrete pancreatic polypeptide

- **Glucagon**
  - When blood glucose is low, α-cells (17%) secrete Glucagon. Makes LIVER break down glycogen into glucose, raising blood sugar.

- **Insulin**
  - When blood glucose is high, β-cells (70%) secrete insulin which inserts GLUT transporter into many cells to be able to absorb glucose.
  - Increases: conversion of glucose to glycogen, uptake of amino acids, synthesis of fatty acids
GONADS – ORGANS THAT PRODUCE GAMETES

Ovaries & Testes

Ovaries
- Produce estrogen and progesterone
- Produce inhibin – inhibits FSH
- Along with placenta, produces relaxin in pregnancy

Testes
- Testes produce testosterone
  - Descent of testes before birth
  - Regulates production of sperm
  - Male secondary sex characteristics (beard growth, deep voice)
  - Inhibin – inhibits FSH

Melatonin

PINEAL
**Pineal**

- The pineal gland secretes **melatonin** from its pinealocytes, changing in response to light.
- Melatonin is derived from **serotonin**, which is derived from the amino acid, **tryptophan**

**Melatonin secretion**

- Visual input (darkness) from the retina in eyes stimulates the **suprachiasmatic nucleus** in the hypothalamus
- The suprachiasmatic nucleus stimulates sympathetic neurons of the **superior cervical ganglion**
- Stimulates pinealocytes to secrete melatonin. Melatonin increases tenfold during sleep.
- Melatonin is a potent **antioxidant**, that counteracts free radicals. Higher levels in children. Causes atrophy of gonads.

**Thymus**

- Immature T-cells do not have a T-cell receptor when they enter the Thymus
- Interaction between immature T cells and thymic cells, cause them to express a T cell receptor and differentiate into either naive CD4 or naive CD-8 cells by the time they exit the thymus.
- T cells also develop **self-tolerance** in the Thymus
**EICOSANOIDS**

- Arachidonic Acid, Leukotrienes, Prostaglandins, Thromboxanes

### Eicosanoid Actions (FYI)

- Eicosanoids bind to receptors on target cells and stimulate or inhibit synthesis of second messengers.
- They break down quickly so they are only in the blood for a short time and in small quantities.

1. **Leukotrienes** stimulate WBC chemotaxis & inflammation
2. **Thromboxane (TX)**, a modified prostaglandin, activates platelets and constricts blood vessels
3. **Prostaglandins** have many actions: smooth muscle contraction, glandular secretion, blood flow, platelet function, respiration, nerve transmission...

**Eicosanoids (20 carbons)**

- Cell membranes contain phospholipids.
- A 20-carbon fatty acid, called Arachidonic Acid can be clipped off from a membrane phospholipid.
- Depending on the enzyme (COX or LOX) that acts on arachidonic acid, it will mainly produce either prostaglandins or leukotrienes.

**STRESS**

Arghhh
Stress and the Thyroid

Stress inhibits production of TSH and conversion of T4 to T3, leading to a hypothyroid state.