### Hormones of Calcium Regulation

Calcium regulation is under the control of 2 hormones, produced by endocrine cells located in rather close proximity to each other.

**ParaThyroid Hormone (PTH)**
- produced by the parathyroid glands

**Calcitonin**
- produced by the parafollicular cells or C-cells

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**Calcitonin**

- Produced by the parafollicular cells of the thyroid glands
- Release of Calcitonin is induced by an increase in plasma Calcium levels.

- This is an example of a humoral control of release (by changes in the composition in the blood).
- There is thus no hypothalamus or Hypophysis control (that would be an example of hormonal control of release).

- **Action** of calcitonin is to
  - inhibit the activity of the osteoclasts
  - stimulates osteoblasts (cells that promote bone formation)
  - result is thus a decrease in plasma calcium levels
ParaThyroid Hormone (PTH)

- Produced by the parathyroid glands
- Located on the posterior side of the thyroid gland; (2 small P.T. glands per lobe)
- The cells in the PT glands that respond to Calcium are called the chief cells.
- Receptors in the chief cells respond to low Calcium levels and induce the release of the PTH
Hormones of Calcium Regulation

Action of PTH is directed to 3 body organs

**Bones**
- increases the number of osteoclasts (cells that break down bone) and their activity
- results thus in enhanced bone breakdown and calcium release

**Kidneys**
- increases the rate at which the kidneys reabsorbs Calcium and magnesium from the renal filtrate (thus more is put back into the bloodstream)
- reduces the re-absorption of phosphate in kidneys, thus promoting phosphate excretion into the urine

Kidneys are also important in the formation of **calcitriol**. Calcitriol is the active form of vitamin D

- Sunlight stimulates keratinocytes in skin to convert a cholesterol derivative into **Vitamin D3 or Cholecalciferol**
- Cholecalciferol is converted in the liver and finally in the kidneys to the hormone **calcitriol**.
- **Calcitriol** is an essential hormone for absorption of calcium and phosphate from the intestine
Gastro-intestinal tract

- Calcitriol increases the rate at which calcium is re-absorbed from the food in the gastro-intestinal tract.

- Without this hormone, a great percentage of dietary calcium is never absorbed by the intestine and lost into the feces.

Crystals of Vit. D

Calcitriol

PTH Regulation

- Plasma calcium
- Parathyroid glands
  - Secretion of parathyroid hormone
  - Increase in plasma
- Bone
  - Resorption
  - Release of calcium into plasma
- Intestine
  - Absorption of calcium
  - Conversion to 1,25-(OH)₂D
  - Plasma
  - Urinary secretion of calcium
- Restoration of plasma calcium toward normal

Image: Crystals of Vitamin D and Calcitriol
### PTH Regulation

**Hypercalcemia**
- Mostly due to primary hyperparathyroidism
- Results in excess bone breakdown
- Results in kidney stone formation

**Hypocalcemia**
- Mostly due to primary hypoparathyroidism because of inadvertent removal of the glands
- Excessive hypocalcemia results in tetanus of respiratory muscles and death

### Abnormalities in Calcium Regulation
Vitamin D deficiency

- Often seen in children not exposed to enough sunlight
- PTH release increases, causing bone breakdown
- End result is deformation of the growing bones

  = Rickets

Hormones of the Adrenal Glands

Adrenal glands are located on top of the kidneys. They have a protective external capsule. The inside consists out of an external cortex area and a central medulla area.
The cortex has 3 areas, composed of different endocrine cells, each producing different hormones with different functions.

The medulla as well is involved in the production of a complete different set of hormones.
All hormones produced in the cortex area of the adrenal gland are steroid hormones. They are all derived from cholesterol via specific pathways that in turn depend on the presence of specific enzymes.

**Hormones of the Adrenal Glands**

<table>
<thead>
<tr>
<th>Androgen</th>
<th>Glucocorticoid</th>
<th>Mineralocorticoid</th>
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<tbody>
<tr>
<td>Androgen</td>
<td>Glucocorticoid</td>
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<tr>
<td>Pregnenolone</td>
<td>17-Hydroxyprogesterone</td>
<td>Androstenedione</td>
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<tr>
<td>Progesterone</td>
<td>Corticosterone</td>
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<td>Cortisol</td>
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**The Mineralocorticoids**

The mineralocorticoids are the hormones produced in the superficial layer of the cortex: the zona glomerulosa

**Aldosterone makes up 95% of the secreted Mineralo-corticooids!**

**Action**

- Aldosterone is instrumental in the control of electrolyte balance, esp. Na⁺ and K⁺
- It indirectly helps with the water balance.
### The Action of Aldosterone

- the action of Aldosterone is on a specific part of the kidney
- stimulates production of Na-pumps in the tubules of the kidney
- the Na-pumps actively re-direct sodium from the forming urine filtrate back into the bloodstream
- the movement of Na+ into the blood stream produces an osmotic effect such that water follows the movement of sodium.
- thus water is re-directed into the blood stream as well
- the movement of Na+ into the blood stream is coupled to movement of K+ out from the blood into the urine

Since aldosterone is a steroid hormone, the effect of aldosterone requires several hours before it will manifest itself (requires new protein synthesis)

### Regulation of Aldosterone secretion

1. Low blood levels of Na$^+$
2. Low blood pressure and low blood osmolarity

- Both conditions result in the release of Renin, a specific Hormone from the kidneys.
- Renin stimulates the formation of Angiotensin I from Angiotensinogen which circulates in the blood.
- In the lungs, blood passes through the lung capillaries where Angiotensin Converting Enzyme converts Angiotensin I to Angiotensin II

Angiotensin II stimulates the adrenal cortex to release Aldosterone

3. High K$^+$ blood levels

- Stimulates the adrenal cortex directly to release Aldosterone
Regulation of Aldosterone secretion

**Low Blood Pressure**

Low Na+

Kidneys $\rightarrow$ **Renin** $\rightarrow$ Angiotensin I $\rightarrow$ Angiotensin II $\rightarrow$ **ACE** (lungs)

High blood K+

Adrenal Cortex $\rightarrow$ **Aldosterone**

Glucocorticoids

Glucocorticoids are produced by the **zona fasciculata**. There are 3 main glucocorticoid hormones:

- Cortisol (95%)
- corticosterone
- cortisone

The functions are numerous but the main function is to **help resist stressors**; adapts our body to stressful situation and helps our body cope.
## Glucocorticoids

### Action

- Inhibits glucose uptake by many tissues (except brain), thus increases blood glucose levels in blood stream for use by the brain.
- Promotes liver to take up A.A. and synthesize glucose (gluconeogenisis)
- Promotes catabolism of proteins in non-essential tissues such as skeletal muscle and uses the A.A. to synthesize glucose (gluconeogenisis)
- Stored proteins are broken down for repair and growth
- Also promotes fat breakdown from fat tissues so that muscle tissues can use fatty acids and glycerol as energy source

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## Glucocorticoids

- Cortisol has a permissive effect in that is enhances vasoconstrictive effect of epinephrine and thus increase blood pressure and circulatory efficiency
- Without Cortisol, a person may go into circulatory shock when stressed due to the lack of a necessary widespread vasoconstriction

Cortisol plays a key role in dealing with stress. The precise role is not know but it obviously involves metabolic shift towards glucose sparing at the expensive of protein breakdown and permissive effects in dealing with blood pressure.
Regulation of Cortisol

Almost any type of stress results in an immediate release of CRH from the Hypothalamus

CRH induces the release of ACTH from the APG

ACTH then acts on the adrenal cortex to release cortisol.

Within minutes of pain and trauma, cortisol plasma levels increase 20 fold.

Excessive Levels of Glucocorticoids

- Excessive levels of glucocorticoids:
  - Depress cartilage and bone formation
  - Inhibit inflammation
  - Depress the immune system
  - Promote changes in cardiovascular, neural, and gastrointestinal function
GonadoCorticoids

GonadoCorticoids are produced by the **zona reticularis**. Main hormones released are the androgens or male sex hormone.

Release is under ACTH control!

- Most gonadocorticoids secreted are androgens (male sex hormones), and the most important one is testosterone.
- Androgens rise significantly between ages 7-13 in both males and females.
- Believed to contribute to:
  - The onset of puberty, including bone and muscle growth, fat deposition
  - The appearance of some secondary sex characteristics
  - Sex drive in females
- Androgens can be converted into estrogens after menopause.
Adrenal Problems

Primary Adrenocortical Insufficiency

- All layers of the cortex are under-secreting
- Usually due to an auto-immune disease

Addison’s disease

- both aldosterone and cortisol are deficient
- hyperkalemia
- excess Na⁺ loss, along with large urine, dehydration, hypotension
- hypoglycemia, sensitive to stressors

Secondary Adrenocortical Insufficiency

- due to a hypothalamic (CRH) or pituitary gland problem (ACTH)
- there is thus a lack of ACTH
- since ACTH mainly controls release of Cortisol and not of aldosterone, this disease is marked by a lack of cortisol
### Adrenal Problems

#### Aldosteronism

- **Hypersecretion of Aldosterone**
- increased Na\(^+\) re-absorption and increased secretion of potassium
- results in excess water retention, hypertension
- if K\(^+\) secretion is severe, low response to stimuli, weak muscle tone, paralysis (hyper polarization of cells)

Can be due to adrenal tumor or overactive secretion of renin (for example, atherosclerotic narrowing of renal arteries)

#### Cushing’s syndrome

- Due to a **Hypersecretion of Cortisol**
- due to 2 possible abnormalities
  - excessive amounts of CRH/ACTH
  - adrenal tumors
- characterized by
  - higher blood glucose levels
  - excessive protein breakdown
  - redistribution of fat from extremities to neck and face
  - increased appetite, high blood pressure
Hypersecretion of adrenal corticosteroids results in a medical condition called Cushing’s syndrome, which includes hypertension (abnormally high blood pressure) and, seen here, “moon face,” with upper-body obesity.

### Congenital Adrenal Hyperplasia

Disorder that results due to a deficiency in enzymes needed for the synthesis of Cortisol

Classical congenital adrenal hyperplasia is rare, affecting only one in 14,000 patients, but mild forms of the disease may occur in one of every 100 to 1,000 persons

Ninety percent of cases of congenital adrenal hyperplasia are the result of a deficiency of the enzyme 21-hydroxylase.
Adrenal Problems

The hallmark of congenital adrenal hyperplasia is inadequate production of glucocorticoids.

Glucocorticoid precursors accumulate in these persons and are diverted and converted to androgenic steroids.

Adrenal Problems

Lack of Cortisol prevents a feedback and ACTH continues to stimulate the adrenal glands, which in turn enlarge (hyperplasia), making more androgenic steroids.

The disorder usually manifests in childhood.

- Hypersecretion of adrenal androgens causes masculinization of the external genitalia of the female fetus.
- In male children, it causes early puberty, deepening of voice, bulky stature (infant Hercules).
- In both sexes, it also results in early closure of epiphyseal plates.
- Children with classic congenital adrenal hyperplasia may lack sufficient amounts of cortisol to mount a stress response, and they frequently succumb to minor illnesses.
Adult women with classic congenital adrenal hyperplasia may have pronounced hirsutism and signs of virilism; they develop secondary male sexual characteristics.