**Calcium Homeostasis**

Calcium homeostasis is regulated by two hormones:

**ParaThyroid Hormone (PTH)**

- Produced by the chief cells in the parathyroid glands (see Fig. 16-11)
- Located on the posterior side of the thyroid gland; (2 small P.T. glands per lobe)
- 2 kinds of cells make up the PT gland:
  - those cells 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
- Action of PTH is directed to 3 body organs (see Fig. 16-12)
  - 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 blood stream)
    - reduces the reabsorption of phosphate in kidneys, thus promoting phosphates excretion into the urine
    - also promotes the formation of calcitriol in the kidneys; calcitriol is the active form of vitamin D (see below)
  - 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.

Vitamin D comes in 2 forms

- Vitamin D2 (cholecalciferol): produced in our skin via the action of UV radiation upon a cholestrol derivative (7-dehydrocholesterol)
- Vitamin D3 (ergocholesterol): a plant derivative

- Vitamin D is converted in the liver to 25 - OH D (25-hydroxyvitamin D)
- In the kidneys, another OH group is attached and it becomes 1,25-OH D or 1,25 - dihydroxyvitamin D or calcitriol. This reaction is catalyzed by 1-hydroxylase, which in turn is induced to activation by the PTH
Calcitonin

- Produced by the parafollicular cells of the thyroid glands (fig. 16-8)
- Release of Calcitonin is induced by an increase in plasma Calcium levels
- 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

This hormone is important in growing children

Clinical Problems

Hypercalcemia
- Common cause is primary hyperparathyroidism

Hypocalcemia
- Often results from thyroidectomy; thus a case of primary hypoparathyroidism
- Can also result from deficient intestinal Vit. D absorption or a problem in making calcitriol. Results in low plasma calcium levels, increased PTH release via parathyroid cells (secondary hyperparathyroidism)

Rickets:
- problem with bone metabolism in children due to Vit. D and calcium deficiencies (children typically are bow-legged due to softness of the bones)
The Adrenal Glands (Fig. 16-13)

These glands are located on top of the kidneys and contain an outer cortex and an inner medulla. The gland is highly vascularized.

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.

- **Cholesterol** → **Pregnenolone**
  - **Progesterone**
  - **17-hydroxyprogesterone**
  - **Dehydroepiandrosterone (A)** (DHEA)
    - **Corticosterone (G)**
    - **Cortisol (G)**
    - **Andostendione (A)**
      - **Aldosterone (M)**

  G = glucocorticoids  M = mineralocorticoids  A = androgens

In the gonads, enzymes to make corticosterone and cortisol are lacking. However, they have additional enzymes that work on androsterone.

**Testes**
- Contain enzymes that convert androsterone to testosterone

**Ovaries:**
- Have Aromatase enzyme; converts DHEA to Estrone and Estradiol. The latter is the major hormone secreted by the ovaries
- Also secrete Progesterone

Males have small amount of female sex hormones and females have small amounts of male sex hormones due to inter-conversions in certain tissues and production in adrenal glands.
1. Adrenal Cortex area

Contains 3 zones with specific cells

- Zona glomerulosa
  - outer zone and cells produce and secrete mineralo-corticoid hormones (they influence mineral homeostasis)

- Zona fasciculata
  - middle zone and produces, secretes gluco-corticoids (affects glucose homeostasis)

- Zona reticularis
  - inner zone right above the medulla and produces the gonado-corticoids
    - these are the sex hormones but the majority produced here are the androgens (male sex hormones)

a. Mineralo-corticoids

- help control water and electrolyte balance, esp. Na and K
- 3 mineralocorticoids are secreted, of which 95% is aldosterone

Action
- Aldosterone reduces excretion of sodium from the body by stimulating sodium re-uptake from the urine back into the bloodstream
- The action is on a specific part of the kidney
- Increased Sodium re-absorption results in increased water retention (thus blood volume and blood pressure effects)
- Aldosterone also results in potassium elimination into the urine

Regulation of Aldosterone secretion is stimulated by (see fig. 16-14)
- Rising blood levels of K⁺
- Low blood levels of Na⁺
- Low blood pressure and low blood osmolarity
- When stressed, CRH and ACTH (see below) are released which have a minor effect but do increase Aldosterone secretion

Clinical manifestation

Due to a hypersecretion or hyposecretion of aldosterone.

Hypersecretion results in
- 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 (hyperpolarization of cells)

Hyposcretion of aldosterone
- excess Na⁺ loss, along with large urine, dehydration, hypotension
- salt cravings, rise in plasma potassium which may cause heart disorders

Typical example of this is Addison’s disease (see below)
b. Glucocorticoids

- There are 3 main hormones in this class: Cortisol (95%), corticosterone and 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.

Cortisol
- Inhibits glucose uptake by many cells, thus increases blood glucose levels in blood stream for use by the brain
- Promotes catabolism of proteins in non-essential tissues such as skeletal muscle and uses the A.A. to synthesize glucose (gluconeogenesis)
- Promotes liver to take up A.A. and synthesize glucose (gluconeogenesis)
- Also promotes fat breakdown from fat tissues so that muscle tissues can use fatty acids and glycerol as energy source
- Stored proteins are broken down for repair and growth
- Cortisol also enhances vasoconstrictive effect of epinephrine and thus increase blood pressure and circulatory efficiency
- At high concentrations (pharmaceutical dosage effect), Cortisol functions as an anti-inflammatory compound
  - reduces number of active cells in the inflammatory response
  - reduces histamine production
  - excess Cortisol suppresses immune system

Control of glucocorticoid secretion is by typical feedback

a. Low levels of glucocorticoids or stress conditions (cold, fasting, starvation, low BP,...)
   stimulates HT which releases Corticotropin Releasing Hormone (CRH)
b. CRH causes the APG to release ACTH
c. The same conditions as in (1) also stimulate APG to release ACTH directly
d. ACTH then works on the adrenal cortex to release the glucocorticoids
e. Rising levels of glucocorticoids feed back to HT and APG to inhibit the release of CRH and ACTH

Cortisol is essential for life
Chronic low levels of cortisol is referred to as adrenal insufficiency
Usually due to a destruction of the cortex area of the adrenal glands = primary adrenal insufficiency.
Can be the result of disease (tuberculosis or an Auto-immune disease)

Example: Addison's disease
- results from a hyposecretion of glucocorticoids. and cortisol
- diminished gluconeogenesis by liver and hypoglycemia
- excess Na+ loss, and potassium imbalance, along with large urine, dehydration, hypotension
- weight loss, anorexia, mental retardation
- extreme sensitivity to stress
- since there is no feedback, levels of ACTH rise and result in skin pigmentation (classic symptom of the disease)
Hypersecretion of cortisol levels

- Due to tumors in adrenal glands (overproduction of cortisol) or pituitary gland (overproduction of ACTH)
- Known as Cushing’s syndrome (see also pages 629-630)
- Characterized by weaker bones, higher blood glucose levels, redistribution of fat from extremities to neck and face, increased appetite, high blood pressure

**c. GonadoCorticoids**

- Principal sex hormones released are the androgens or male sex hormone
- Small amounts of estrogens are released as well
- Function of adrenal androgens in the male is rather unimportant since testosterone, produced by the testis, is 5 times more potent
- Adrenal androgens are however a main source of male sex hormones in the female
- Some adrenal androgens are converted to estrogens in the blood and accounts for the occurrence of female sex hormones in the adult male

- The secretion of adrenal gonadocorticoids is stimulated by ACTH (and not by pituitary gonadotropins such as FSH, LH)

**Functions**

- Under normal conditions, the effects are mainly metabolic
- The effect are on bone growth, muscle growth, fat deposition in children between 7-15 (marked surge in adrenal androgens)
- Disturbances bring about dramatic changes

**Example: Congenital Adrenal Hyperplasia**

- Genetic disorder that results in low enzymes needed for the synthesis of Cortisol
- Low blood Cortisol levels stimulates increased ACTH secretion
- This stimulates growth and secretion of adrenal cortex; enlarged adrenal gland
- Precursor molecules that normally go into formation of Cortisol now go into formation of excess androgens
- If this occurs in the adult woman, secondary male characteristics develop: body and facial hair, muscle growth, voice changes, genital changes, breast atrophy; this is known as Virilism
- If this occurs in young boys, early male sexual developments occurs and growth is stunted = infant Hercules syndrome
2. Adrenal Medulla Area

- Contains Chromaffin cells which are modified postganglionic sympathetic neurons
- They are activated by sympathetic nerve fibers
- They secrete the catecholamines epinephrine and norepinephrine: 85% of what is secreted is epinephrine
- Epinephrine works on heart and metabolic activities while norepinephrine is more of a peripheral vasoconstrictor
- Stress activates sympathetic nervous system which thus induces medulla to release the catecholamines

This Results in
- increased Blood pressure and heart rate
- liver converts glycogen to glucose and releases it into blood stream
- bronchioles dilate, decreased digestive activity, increased overall metabolic activity in brain, heart and muscles
- Effect is (relatively) short term as catecholamines are rapidly broken down

The interrelationship between stress, the hypothalamus, the adrenal glands, metabolic changes and the adrenaline rush we experience should now become clear and is nicely shown in FIG 16-16.