Endocrinology - study of hormones

1. Endocrine System - system of widely scattered endocrine glands that produce hormones that help control body activities and maintain homeostasis; it also includes hormone-secreting cells within a variety of organs to include the heart, brain, stomach, kidneys, skin, and small intestine.

2. Body Integration - The activity of various organ systems must be closely coordinated or integrated to benefit the whole organism. Integration involves an exchange of information from one body system to another. There are two integrative systems in the body: Nervous and Endocrine
   a. Nervous System - consists of a network of neurons that are capable of reacting rapidly to a stimulus (often within 1-10 msec) and bringing about a response such as muscle
contraction or glandular secretion. Neurons relay information as nerve impulses and the effects tend to be short-lived (seconds to minutes)

b. **Endocrine System** - Generally, the release of hormones act to change the metabolic activities of cells. The endocrine system relays information by way of hormones that travel in the bloodstream. The endocrine system tends to react more slowly to a stimulus, often taking seconds to days. Unlike the nervous system, the effects of hormones tend to last for hours, days, or weeks.

**Endocrine Glands** - mass of epithelial cells or specialized neurons (neurosecretory cells) that manufacture and secrete hormones into the interstitial fluid and from there into the bloodstream.

1. Hormones are **distributed by way of the bloodstream** to capillary beds in all parts of the body
2. Hormones act only on their **target cells**. Target cells are associated with target organs.
   a. **Target cells possess hormone-specific receptors**.
   b. Cells that respond to hormones possess **receptors** for that hormone. Hormones affect *only those cells to which they can bind to a specific receptor*.
   c. For example, insulin likely encounters every cell in the body, but only has an impact on those cells that possess insulin receptors. One of insulin's effects is to promote the facilitated diffusion of glucose into skeletal muscle and fat cells.
   d. Receptor defects are associated with several endocrine disorders.
3. Hormones are powerfully effective even at extremely low blood concentrations.

**Action of Hormones**

1. Hormones act like switches to turn certain metabolic pathways on or off
2. **binding of a hormone to its receptor** acts in a variety of ways that often affect the production and/or activity of enzymes or the **transport of materials** across the plasma membranes of cells.
3. **Glucagon**, for example, stimulates enzymes in liver cells that break glycogen down to release glucose molecules (glycogenolysis).
4. **Growth hormone** stimulates the uptake of amino acids by certain cells of the body.
Chemistry of Hormones - there are three major classes of hormones, each with a unique molecular structure

1. Steroid
   a. All steroid hormones are synthesized from cholesterol and are lipid soluble. They include testosterone, the estrogens, and progesterone, as well as cortisol and aldosterone.
   b. Hydrophobic (lipophilic): steroids are not soluble in blood plasma. Once secreted into blood plasma, they bind to transport proteins. Albumin is an example of a protein that is made in the liver that binds to and transports steroids within the blood.

2. Peptides (proteins)
   a. chains of amino acids that are usually less than 200 amino acids in length
      1. peptide hormones are arbitrarily defined as those with 2 to 50 aa’s, whereas proteins have more than 50 aa’s. Avg length of a protein is around 480 aa’s.
      2. in general, most hormones are referred to as peptide hormones to include GH (191 aa) and insulin (51 aa).
   b. e.g., ADH and OXT (these are small peptides that are only 9 amino acids in length)
   c. insulin is made up of 51 aa’s and growth hormone consists of 191 aa’s
   d. water soluble (hydrophilic, lipophobic)

3. Amine (monoamines, amino acid derivatives) - modified aa’s
   a. simple hormones that are synthesized from aromatic amino acids (e.g., tyrosine, phenylalanine, and tryptophan). For example, tryptophan makes serotonin.
   b. Catecholamines
      1. these are a subclass of amines that are synthesized from the amino acid tyrosine;
      2. they include epinephrine (adrenaline), norepinephrine (noradrenaline), and dopamine
   c. thyroid hormone is a monoamine. It is an iodinated derivative of tyrosine, but it is not considered to be a catecholamine.
Mechanism of Hormone Action - Hormones interact with target cells in one of two major ways

1. **Peptide hormones and catecholamines**
   a. bind to membrane receptors and act through intracellular second messengers
   b. peptide hormones include glucagon, parathyroid hormone, and ADH cannot pass through the lipid bilayer of cell membranes.
   c. Instead, they bind to a receptor (usually GPCR) on the plasma membrane and trigger the production of a "second messenger" in the cytoplasm which brings about the hormone's effect on the target cell.
   d. The most important second messenger is cyclic AMP (cAMP).
   e. cAMP forms when a hormone binds to a GPCR membrane receptor which stimulates a G protein to activates an enzyme in the membrane called adenylyl cyclase. This enzyme converts ATP to cAMP.
   f. cAMP then modifies the activity of existing enzymes (usually kinases) to bring about the target cell responses.
   g. kinases phosphorylate pre-existing inactive enzymes making them active. The activated enzymes catalyze reactions that carry out the hormone’s response in the cell.

2. **Steroid Hormones**
   a. steroids act by binding to receptors inside cells that are found in the cytoplasm or the nucleus
   b. Unlike the peptide hormones, the steroid hormones (e.g. testosterone, estrogens, progesterone, cortisol) are lipid-soluble molecules that readily diffuse through cell membranes. Once inside the cytoplasm, steroid hormones bind to receptors to form hormone-receptor complexes (HRC). The HRC’s enter the nucleus if they form first in the cytoplasm.
   c. Steroid hormone-receptor binding leads to the formation of a complex (HRC) that acts as a transcription factor.
      1. the transcription factor (steroid bound to receptor) then binds to the promoter region of a gene on a chromosome in the nucleus
      2. the transcription factor (HRC) activates the gene
   d. Gene transcription results in mRNA molecules that when translated in the cytoplasm produce enzymes (protein synthesis) or structural proteins that set into motion the hormone's observed effect.
### TABLE 7-1 Chemical Classification of Vertebrate Hormones

<table>
<thead>
<tr>
<th>Properties</th>
<th>Peptides</th>
<th>Amines</th>
<th>Steroids</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Structure</strong></td>
<td>Chains of specific amino acids, for example:</td>
<td>Catecholamines</td>
<td>Cholesterol derivative, for example:</td>
</tr>
</tbody>
</table>
|                    | Cys
|                    | Tyr
|                    | Pro
|                    | Arg
|                    | Gln
|                    | (Vasopressin)                                | Thyroid Hormone                           | Lipophilic (hydrophobic)                        |
| **Solubility**     | Hydrophilic (lipophobic)                      | Hydrophilic (lipophobic)                 | Stepwise modification of cholesterol molecule in various intracellular compartments |
| **Synthesis**      | In rough endoplasmic reticulum; packaged in Golgi complex | In cytosol                               |                                               |
| **Storage**        | Large amounts in secretory granules           | In chromaffin granules                   | In colloid                                    |
| **Secretion**      | Exocytosis of granules                        | Exocytosis of granules                   | Not stored; cholesterol precursor stored in lipid droplets |
| **Transport in Blood** | As free hormone                               | Half bound to plasma proteins            | Mostly bound to plasma proteins               |
| **Receptor Site**  | Surface of target cell                        | Mostly bound to plasma proteins          | Mostly bound to plasma proteins               |
| **Mechanism of Action** | Channel changes or activation of second-messenger system to alter activity of preexisting proteins that produce the effect | Activation of second messenger system to alter activity of preexisting proteins that produce the effect | Activation of specific genes to produce new proteins that produce the effect |
| **Hormones of This Type** | All hormones from the hypothalamus, anterior pituitary, posterior pituitary, pineal gland, pancreas, parathyroid gland, gastrointestinal tract, kidneys, liver, thyroid C cells, heart | Only hormones from the adrenal medulla     | Hormones from the adrenal cortex and gonads plus most placental hormones (vitamin D is steroid-like) |

(Thyroxine, T4)
Major Endocrine Glands (7)

1. **pituitary** (also called the hypophysis)
   a. anterior (adenohypophysis): FSH, LH, GH, PRL
   b. posterior (neurohypophysis): OXT, ADH

2. **thyroid**: thyroid hormone, calcitonin (CT)

3. **parathyroid**: PTH

4. **adrenal gland**: cortisol, aldosterone, epinephrine (Epi), adrenal androgens (e.g., DHEA, testosterone)

5. **pancreas**: insulin (INS), glucagon (GCG)

6. **gonads** (organs that make gametes, sperm and egg)
   1. **testis**: testosterone (T)
   2. **ovary**: estrogen (E), progesterone (T)

7. **Other endocrine glands** include the **skin** (Vitamin D), **heart** (atrial natriuretic hormone), **stomach** (gastrin), **small intestine** (secretin and cholecystokinin), **kidneys** (erythropoietin), and **liver** (somatomedins).
Pituitary Gland and the Hypothalamus

1. The pituitary gland is a **bilobed** structure
2. sits in the **sella turcica** of the **sphenoid** bone and hangs by a stalk called the **infundibulum** from the **hypothalamus** of the brain.
3. The pituitary gland consists of **2 structures**:
   a. the **anterior and posterior pituitaries**.
   b. The two pituitaries are treated as if they are a single gland, but they actually arise independently in the embryo and have entirely separate functions.
4. **Anterior Pituitary** (adenohypophysis)
   a. The anterior portion of the gland (**anterior pituitary or adenohypophysis**) consists mostly of epithelial cells that secrete peptide hormones (FSH, LH, PRL, GH, and others) in **response** to releasing and inhibiting hormones from the **hypothalamus**.
   b. It is connected to the hypothalamus by the **hypophyseal portal system** (HPS) that is found mostly in the **infundibulum**. The HPS is also called the **hypothalamo-hypophyseal portal system** (HHPS)
   c. **portal system** – blood vessels (veins) that connect 2 capillary beds
5. **Posterior Pituitary** (PP, neurohypophysis)
   a. Contains the **axonal endings** of **neurosecretory** cells whose dendritic zones are found in the **hypothalamus**.
b. When the dendritic zones of these **hypothalamic** neurosecretory cells are stimulated, **oxytocin** and **ADH** are released from their **axonal** endings in the **posterior pituitary (PP)**.

1. Hypothalamic neurons from supraoptic nucleus (SON) secrete ADH from PP
2. Hypothalamic neurons from paraventricular nucleus (PVN) secrete OXT from PP

6. **Hypothalamus**
   a. the hypothalamus produces **hormones that regulate the release of anterior pituitary hormones**
   b. most of the hypothalamic hormones are **releasing hormones** that stimulate the anterior pituitary to secrete hormones (TRH, CRH, GnRH, PRH, GHRH)
   c. some the hypothalamic hormones are **inhibiting hormones** that suppress the release of anterior pituitary hormones (e.g., PIH)
   d. the **hypothalamus also makes OXT and ADH that are secreted by the posterior pituitary**

7. **Releasing and inhibiting hormones from hypothalamus** (mostly peptide hormone, although PIH is dopamine)
   a. **TRH** (thyrotropic-releasing hormone) – stimulates release of TSH
   b. **CRH** (corticotropin-releasing hormone) – stimulates release of ACTH
   c. **GnRH** (Gonadotropin-releasing hormone) – stimulates release of FSH and LF
   d. **GHRH** (Growth Hormone releasing hormone) – stimulates release of GH
   e. **PRH** (Prolactin-releasing hormone) – stimulates release of PRL
   f. **PIH** (Proloactin-inhibiting hormone) – inhibits the release of PRL
Hypophyseal portal system (HPS) or Hypothalamic-Hypophyseal Portal System (HHPS)

1. portal system of blood vessels connect two capillary beds (another portal system in the body is the hepatic portal system)
   a. capillaries in hypothalamus drain into small portal veins that deliver blood to capillaries in AP
   b. capillaries in the AP lead to veins that are part of the general circulation

2. releasing and inhibiting hormones are released from the axonal endings of neurosecretory cells in the hypothalamus into capillaries of the hypophyseal portal system
   a. the axons of neurosecretory cells in the hypothalamus terminate on the capillaries
   b. hypothalamic hormones travel by the way of the hypophyseal portal system to capillaries in the AP
   c. hypothalamic hormones leave capillaries in AP and stimulate or inhibit the glandular epithelial cells of the AP

Anterior Pituitary (FSH, LH, PRL, GH, TSH, ACTH)

1. Gonadotropins
   a. FSH: males - stimulates spermatogenesis; females - stimulates maturation of ovarian follicle at onset of proliferative phase of menstrual cycle
   b. LH: males - stimulates leydig cells to secrete testosterone (also called ICSH); females - induces ovulation during the menstrual cycle

2. PRL (prolactin)
   a. male (minor role): makes the Leydig cells of the testes more sensitive to LH, thus enhances the secretion of testosterone
b. **female** (lactation means to make breast milk)

1. Stimulates and sustains **milk production** in the cells of the lactating breast after childbirth.
2. **Suckling of the infant** on the richly innervated teat of the breast sets up a neural reflex that triggers the anterior pituitary to release PRL. In the absence of suckling, the breasts stop producing milk.
3. **Amenorrhea** during breast feeding can continue for 2-3 years if mother exclusively breast feeds. High levels of circulating PRL inhibits the release of FSH and LH, thus shutting down the menstrual cycle. PRL’s effect deteriorates over time and cannot always be used as a reliable means of birth control.
4. **Oxytocin (OXT)** is another pituitary hormone involved with lactation (discussed later).
3. **Growth Hormone** (GH) - GH acts on most cells of the body (panmetabolic). The pituitary produces about 1000x more GH than any of the other pituitary hormones
   a. **Major effects** on the following organs
      1. skeletal muscle
      2. adipose (fat cells)
      3. liver
      4. growth plates of long bones during growth years

   ![Chemical diagram of fatty acid metabolism](image)

   b. **Fat metabolism**
      1. GH stimulates **lipolysis** of triglycerides in adipocytes (TG -> 3FA’s + glycerol)
      2. this leads to an increase in the number of **circulating fatty acids** (FA)
      3. **FA’s** (16-18 C) are taken up by cells of the body and used to make ATP by cellular respiration
      4. **Beta oxidation**
         a. β-ox is the catabolic process by which FA’s are broken down in the mitochondria to Acetyl-CoA which enters the Krebs cycle
         b. acetyl-CoA eventually broken down to CO2 + H2O as ATP forms during aerobic stages of cellular respiration
         c. **Palmitic acid** (16 C)/2 = 8 AcCoA. In each round of beta-oxidation an Acetyl-CoA is produced.
         d. One FA yields around 100 ATP (approx. 10 ATP/AcCoA), whereas glucose only gives around 32 ATP
      5. many tissues decrease their use of glucose when FA’s are available for ATP synthesis
c. Carbohydrate metabolism
1. GH stimulates hepatic glycogenolysis (breakdown of glycogen in the liver)
2. this leads to an increase in the circulating levels of blood glucose
3. glucose is taken up by cells of the body and used to make ATP by cellular respiration
4. GH decreases glucose uptake by resting skeletal muscle cells
   a. GH has a glucose-sparing effect
   b. GH decreases the use of glucose by resting skeletal muscle (40% of body mass)
   c. this increases the availability of glucose for brain neurons
   d. resting skeletal muscle cells maintain their BMR by oxidizing more FA’s as compared to glucose
d. Protein metabolism
1. GH stimulates amino acid uptake by fac df (decreasing amino acids in plasma)
2. GH stimulates protein synthesis
e. Growth Plates of Long Bones (called epiphyseal plates)
1. GH stimulates growth of the hyaline cartilage in the growth (epiphyseal) plates. GH stimulates the mitotic division of chondroblasts and chondrocytes which build cartilage
2. this allows the long bones to grow longer (elongation) during childhood
3. at some point in time the EP “close”; this occurs as the rate of ossification exceeds the rate of new cartilage growth and the cartilage completely ossifies
   a. ossification of all of the hyaline cartilage in the EP causes it to stop growing
   b. this stops bone elongation and means that a person has reached their adult height
   c. time of growth plate closure
      1. 14-16 in girls (around 10th grade): estrogen secretion from the ovaries during menstrual cycles that start around the age of 12 inhibit growth of the cartilage; girls often reach their adult height about 3 years after their first period
2. **18-21 in boys**: testosterone from the testes of boys inhibits the growth of cartilage in EP but not as much as estrogen

f. **Stimuli that Trigger the Release of GH**
   1. **Amino acids in diet**: Increases in the amino acid concentration of plasma stimulates the release of growth hormone.
   2. **decreases in fatty acids** in the blood between meals stimulates GH release, hence lipolysis

g. **GH Pathologies**
   1. **Pituitary Dwarfism** (also called Little People)- low GH during growth years; early closure of epiphyseal plates that decreases bone elongation; dwarfism is defined as an adult height less than 4’10”. There are about 200 medical disorders that can cause dwarfism
   2. **Pituitary Gigantism** - too much GH during the growth years; proportions tend to be normal but oversized; giants are typically between 7’ and 9’ tall. Hypersecretion of GH that is usually caused by a pituitary tumor gives rise to gigantism. Experience a lot of physical problems and die young

   a. **Robert Wadlow** (American) is the tallest man to ever live. He died at the age of 22. At death he was 8’11” tall and weighed 439 lbs (wore a size 37 shoe). He was still growing at the time of death. He toured with a circus as a side show.

<table>
<thead>
<tr>
<th>Age</th>
<th>Height</th>
<th>Weight (lbs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 (birth)</td>
<td>1’0”</td>
<td>8 lb 6 ounces</td>
</tr>
<tr>
<td>1</td>
<td>3’0”</td>
<td>45</td>
</tr>
<tr>
<td>2</td>
<td>4’6”</td>
<td>75</td>
</tr>
<tr>
<td>4</td>
<td>5’4”</td>
<td>105</td>
</tr>
<tr>
<td>6</td>
<td>6’0”</td>
<td>160</td>
</tr>
<tr>
<td>12</td>
<td>7’2”</td>
<td>287</td>
</tr>
<tr>
<td>18</td>
<td>8’4”</td>
<td>391</td>
</tr>
</tbody>
</table>

   b. **Anna Baker** is one of the tallest female at 7’5”. She married and gave birth to a 23 lb baby who was 30” long that only lived for 11 hrs. Anna died at the age of 42 from heart failure. She and her husband (another giant) toured with a circus as a side show.

<table>
<thead>
<tr>
<th>Age</th>
<th>Height</th>
<th>Weight (lbs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>4’6”</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>5’2”</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>6’2”</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>7’0”</td>
<td>394</td>
</tr>
</tbody>
</table>

   c. **Zeng Jinian** (China) is the tallest woman in the world. She died at the age of 18. She grew to be 8’ 1¾”. She is the only female to be among the 16 people to reach 8’ in height.

3. **Acromegaly** - too much GH in adult that leads to thickened bones (hands, feet, jaw, skull); can lead to headaches from compression on the brain from inward growing skull bones
Sandy Allen, 7’7” tall

Svetlana Pankrtova’s legs rise a whopping 52 inches while He Ping Ping measures at just 29 inches tall. Svetlana is 6’7” tall.

Bao, who stands 2.36 meters (7.9 feet) tall, and He, who only reaches 73 centimeters (2.4 feet) in height.
1 The paraventricular and supraoptic nuclei both contain neurons that produce vasopressin and oxytocin. The hormone, either vasopressin or oxytocin depending on the neuron, is synthesized in the neuronal cell body in the hypothalamus.

2 The hormone travels down the axon to be stored in the neuronal terminals within the posterior pituitary.

3 When the neuron is excited, the stored hormone is released from the terminals into the systemic blood for distribution throughout the body.
Posterior Pituitary (OXT and ADH)

1. the dendritic zones (cell bodies and dendrites) of neurosecretory cells found in the hypothalamus (supraoptic and paraventricular nuclei) release OXT and ADH at their axon terminals in the posterior pituitary
   a. the axons of the neurosecretory cells extend down the infundibulum and into the posterior pituitary where they end at their axon terminals
   b. ADH and OXT are synthesized in the cell bodies of hypothalamic neurons and packaged into vesicles
      1. Supraoptic nucleus in hypothalamus contains neurons that synthesize ADH
      2. Paraventricular nucleus in hypothalamus contains neurons that make OXT
   c. the hormone-containing vesicles are then transported down the axon by axoplasmic flow along microtubule paths to the axon terminals. The axons go down the infundibulum and end in the posterior pituitary
   d. the axon terminals contain only one of the two hormones
      1. some neurons contain ADH and others contain OXT, but not both
      2. the hormones can be released independently of each other
   e. stimulation to the cell bodies of the neurosecretory cells in the hypothalamus results in nerve impulses that travel to the axon terminals and stimulate the release of the hormones from the PP by exocytosis into the blood
2. **Oxytocin (OXT)**
   
a. **males** and non-pregnant females – OXT plays a role in sexual arousal and orgasm. OXT release during sex appears to provide a pleasureable sense of sexual satisfaction. In nonsexual relationships, OXT release promotes affectionate behavior.
   
b. **females**: two major effects associated with labor and breast feeding
   
   1. **Labor**: stimulates **labor contractions** at birth (contractions of the smooth muscle of the uterine myometrium) to push the baby out of the uterus
   
   2. **Milk Let-Down**: stimulates the cells of the breast to **move breast milk** out of holes in the teat into **mouth of suckling baby** (milk ejection). Prolactin (PRL) from the AP stimulates breast cells to make and store milk.
   
c. **Myometrial Contractions at Parturition or Labor** (i.e. stimulate labor contractions)
   
   1. **at birth** the child’s head is pressed into the **cervical** region of the uterus which causes the cervix to **stretch**. **Dilation** of the cervix triggers a neural reflex via stretch receptors that travels to the hypothalamus to stimulate the release of **oxytocin** from the posterior pituitary.
   
   2. **OXT** is a **powerful stimulator** of the **myometrial** smooth muscle. OXT induces labor **contractions** that push the baby out of the uterus and into the vagina.
   
   3. **Pitocin** is a synthetic OXT-like compound used in hospitals that is given by IV-drip to stimulate myometrial contractions that decrease the amount of time a woman spends in labor.
   
   4. Oxytocin is also given **after birth** to cause the **uterus** to **regress** in size as it contracts and squeeze uterine blood vessels, thus minimizing the danger of hemorrhaging.
   
   d. **Lactation**
   
   1. The **suckling** of the infant on the female teat triggers a neural reflex that stimulates the release of OXT from the posterior pituitary.
   
   2. OXT stimulates myoepithelial cells in the breast to contract which squeezes milk out of the glandular cells through the ducts of the breast and into the mouth of a baby.
This process, which relies on OXT release, is called "milk let-down." It occurs **30 seconds** to 1 minute after suckling begins.

3. The release of OXT and the milk let-down reflex can be conditioned to such events as crying. **Stress** inhibits the release of oxytocin and can **interfere** with breast feeding.

4. Both oxytocin and prolactin are needed for breast feeding. PRL stimulates the glandular epithelial cells to make milk and OXT stimulates the cells to release their milk into ducts that lead to openings in the teats.

   e. **OXT in both sexes:** Affectionate hugging stimulates the release of OXT from the posterior pituitary in both sexes. OXT acts back on the mood centers in the brain to make us feel good. OXT appears to play a role in maintaining relationships and social bonds. People who have positive relationships with their partner have higher OXT levels. People who get lots of hugs at home tend to have the highest OXT levels.

3. **Antidiuretic Hormone** (ADH, also called VP or vasopressin)
   
   a. **2 major effects**
      1. **decreases the volume of body water that the kidney puts into the urine,** thus **decreasing the volume of urine**
         a. this helps to **prevent the loss of body water** in the urine when **dehydrated** (e.g., sweat a lot while exercising or go for a while without drinking)
         b. **antidiuretic effect** (diuresis means to make urine)
         c. ADH helps a person conserve body water until they take a drink. It doesn’t add any water to the body or prevent urination. It doesn’t solve the problem of dehydration. That problem can only be solved by replacing fluids by drinking. The body must always make some urine to get rid of metabolic waste products like ammonia, urea, and uric acid. N-containing waste products like ammonia are toxic to neurons.
2. causes the **contraction of the smooth muscle cells** in the walls of **arterioles** that produces moderate **vasoconstriction**; this **increases the blood pressure** to a slight degree (vasopressor effect)

b. **Regulation of ADH release** (osmolarity of blood plasma)
   
   1. osmoceptors in hypothalamus respond to changes in osmolarity of plasma to increase or decrease ADH release from PP

2. **Dehydration**
   
   a. **ADH is released** from the posterior pituitary when there is an **increase** in the osmolarity of blood plasma.

   1. **osmolarity** – number of osmoles (Osm) of solute per liter of solution (Osm/L)
   
   2. **osmoles** - the number of moles of solute that contribute to the osmotic pressure of a solution

   3. the blood becomes **hypertonic** as the osmolarity increases (indication that there is too little water in the fluid compartments of the body which tends to concentrate plasma solutes).

   4. hypertonic blood increases the osmotic pressure of plasma

   Osmotic Pressure $\alpha$ [solute]

b. **Dehydration Causes**
   
   1. one goes **without drinking** for more than several hours or during physical activity in which a lot of sweat is given off.

   a. lose water by sweating, urine and when exhale
   
   b. must replace water loss or become dehydrated (negative water balance)

   2. Elderly can go without drinking for long periods

   3. **chronic diarrhea**

   4. **hemorrhaging (blood loss)**

   c. **ADH helps prevent water loss** in urine until rehydrate

3. **Overhydration** - Excess body water makes the blood hypotonic (decrease in osmolarity) which shuts down ADH release and encourages urine production.
Thyroid Gland

1. Introduction
   a. found below the larynx (voicebox) and over the trachea in the neck.
   b. Cells of the thyroid gland secrete two major hormones
      1. thyroid hormone (actually a collective name for two hormones: T₃ - triiodothyronine, and T₄ - thyroxine)
         a. T₃ and T₄ are secreted by the thyroid gland.
         b. T₄ (thyroxine) is considered to be a prohormone since it is converted by cells to T₃ the biologically active form
         c. T₄ is converted to T₃ in target cells and in liver by iodothyronine deiodinase. T₃ is the final form of the hormone in cells
   2. Calcitonin (CT) – helps to regulate the calcium ion concentration of the blood

2. Thyroid hormone (TH) - The thyroid gland secretes mainly lipid-soluble (hydrophobic) thyroxine into the bloodstream which is transformed into triiodothyronine within target cells. It is the latter hormone that actively affects target cells.
   a. Iodine (iodine in the diet is required for thyroid hormone synthesis)
      1. Thyroid hormone is the only chemical in the body that contains iodine in its structure. Thyroid hormone is made from tyrosine, then iodinated
2. **Iodine** is an essential dietary mineral that is found in most vegetables and seafood (NaI salt).

3. Iodine exists as iodide ions (I') in solution. Thyroid gland cells have **iodide ion active transport** pumps to move iodide ions across their plasma membranes.
   a. iodide is carried into the cell by a secondary **active transport symport pump**
   b. a **protein carrier** cotransports iodide ions and Na+ into the cell. Na+ move by facilitated diffusion while the I- move by secondary active transport.
   c. the Na+ diffusion gradient is set up by a primary **active transport antiport pump** for Na+/K+

4. Iodide ions are attached to the amino acid **tyrosine** to make T₃ and T₄.
   b. thyroid hormone (T₃ and T₄) is **lipid-soluble** so after it is released from thyroid gland cells it **binds to plasma proteins; both hormones are secreted by the thyroid gland**
   1. the specific binding protein is called **thyroxin-binding globulin** (TBG)
   2. despite the name, **TBG binds to both T₃ and T₄**

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4. **Mechanism of Action**
   1. thyroid hormone **affects almost every cell** in the body
   2. thyroid hormone moves through the **plasma membrane** by an ATP-dependent carrier protein, then **moves** into the **nucleus** where it binds to a **nuclear receptor** (thyroid hormone receptor)
   3. this **binding** (thyroxin to receptor) **stimulates the transcription** of **genes** to make mRNA that leads to the synthesis of new proteins
   4. the activated genes **synthesize enzymes** that carry out the hormones effect on the cell

5. **Effects of thyroid hormone**
   a. **maintain** the BMR (basal metabolic rate)
      1. BMR is the **resting rate of chemical activity** that occurs in cells
      2. BMR sometimes thought of as the “**idling speed**” of the body
3. if the BMR is too low, then thyroid hormone stimulates enzyme activity in the mitochondria that leads to an increase in ATP synthesis to increase the BMR
4. thyroid hormone helps to maintain a resting level of ATP synthesis in order to run ATP-dependent activities
5. the metabolic rate of cells is directly proportional to ATP synthesis which is directly proportional to O2 uptake by cells (cellular respiration)
b. helps to generate heat in order to maintain the resting body temperature (37C, 98.6F) by stimulating the mitochondrial phase of cellular respiration.
1. The breaking of covalent bonds during cellular respiration releases heat
2. blood picks up heat as it circulates through organs (especially skeletal muscle) and distributes heat throughout the body

c. increases O2 consumption by cells since O2 is used in mitochondria as the terminal e acceptor for cellular respiration
d. increase lipolysis to provide FA’s for ATP production by cellular respiration
e. Thyroxine stimulates the development of the brain, especially during pregnancy and the first six months of life.

6. Pathologies of Thyroid Hormone
a. hypothyroidism
1. underactive thyroid resulting in low levels of thyroid hormone
2. causes
   a. failure of thyroid gland cells to secrete thyroid hormone
   b. decreased output of TRH (hypothalamus) and/or TSH (AP)
   c. deficiency of iodine in the diet (lack of iodide salts)
3. symptoms
   a. decrease BMR which will decrease ATP synthesis in target cells
   b. weight gain since don’t burn off as many organic fuel compounds (FA’s, glucose, amino acids) to make ATP as normal
   c. easily fatigued (feel very tired all of the time)
   d. slow reflexes
   e. not very alert and poor memory (mental slowness) – e.g., takes a while to process a question before answering
   f. lower than normal body temperature (not tolerant of cold because can’t generate enough body heat to compensate)
4. treatment
   a. hormone replacement therapy (HRT)
   b. take thyroid hormone for life
5. Cretinism (also called congenital hypothyroidism)
   a. hypothyroidism in newborn that if allowed to persist for several years causes stunted growth
   b. depressed BMR (sluggishness) by as much as 40%
   c. severe mental retardation because homeostatic levels of thyroid hormone are necessary for proper development of the brain.
d. babies are tested at birth for adequate thyroid function. Newborns diagnosed with hypothyroidism are given hormone-replacement therapy for life. The hormone can be taken orally.

b. hyperthyroidism
1. overactive thyroid gland that secretes a lot of thyroid hormone
2. symptoms
   a. elevated BMR
   b. generate excess body heat that leads to excess sweating
   c. increased appetite with loss of body weight since burn off fuel molecules at faster than normal pace (despite increase appetite and greater food intake)
   d. heart rate may increase to dangerous levels
   e. insomnia (difficulty sleeping)
3. treatment
   a. drugs that suppress the synthesis and secretion of thyroid hormone
   b. surgically remove a portion of the gland
   c. inject radioactive iodine that is taken up by the cells of the thyroid gland as a way of killing some of the cells
   d. treat pituitary if source of problem is a pituitary tumor making too much TSH
Three hormones regulate Ca2+ concentrations in blood plasma

1. **Three hormones**
   a. **Calcitonin (CT)** – secreted by thyroid gland; acts to decrease [Ca2+] in blood
   b. **Parathyroid hormone (PTH)** – secreted by parathyroid gland; acts to increase [Ca2+] in blood
   c. **vitamin D** (steroid hormone made by skin cells that is also called *cholecalciferol*) – secreted by epidermal cells of the skin; acts to increase absorption of Ca2+ from food in intestine

2. **Calcium** in the body (calcium exists as Ca2+ in body fluids)
   a. **most Ca2+** (99%) is found in hard rock-like crystals of **Ca3(PO4)2** (85% hydroxyapatite) in the matrix of **bones and teeth, as well as, Ca(CO3)2** (15%).
   b. the **rest of the Ca2+ is found inside cells or in plasma** and the interstitial fluid (IF)
      1. this is the **free Ca2+ pool**
      2. it is the calcium that gets regulated
3. What does Ca2+ do in body?
   a. structural component of **bones and teeth**; solid crystals of mostly Ca3(PO4)2
   b. triggers the **exocytosis** of **neurotransmitters** at synapse and the exocytosis of **peptide hormones** from glandular epithelial cells
   c. participates in **many reactions** within cells. Ca2+ are often **cofactors** that bind to and activate enzymes. A cofactor is a non-protein chemical that is required for enzyme activity. Coenzymes are a type of cofactor. Inorganic **cofactors are usually metal ions** like Ca2+. Organic cofactors are often modified vitamins (e.g., NAD, FAD, CoA)
   d. **essential to muscle contraction**
      1. Ca2+ are the **intracellular trigger** for **muscle contraction**
      2. Ca2+ **bind to troponin** to shift tropomyosin off binding sites on the actin myofilaments so that the cross bridges on myosin myofilaments can form rigor bonds in order to shorten sarcomeres
   e. essential for the **clotting of blood**

3. **Hypocalcemia and Hypercalcemia** (must regulate calcium in blood) – 2 conditions that occur if [Ca2+]b is not regulated
   a. **Hypocalcemia** – **chronically low levels of calcium** ions in the blood
      1. **skeletal muscles** can start to **contract uncontrollably** (twitching)
      2. this can make it **difficult to contract the diaphragm** (breathing problems that lead to **suffocation** and death)
   b. **Hypercalcemia** – **chronically high levels of calcium** ions in the blood
      1. produces **cardiac arrhythmias** (irregular heart beats)
      2. this can lead to **cardiac arrest and death**

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**Osteoblasts and Osteoclasts** (type of bone cells that live on surface of bone)

1. **Osteoblasts** (bone-forming cells) – make the **osteoid** = ground substance + collagen fibers
   a. cells that **live on the surface of bone** that are involved in **bone deposition**
   b. bone deposition occurs as osteoblasts secrete **collagen** fibers and **glycoproteins**. The **glycoproteins** mix with the **interstitial fluid** to form a solution called the **ground substance**
c. **Osteoid** = ground substance (viscous solution) and collagen fibers (like rebar in concrete). **Osteoid** is the unmineralized part of bone consisting of collagen fibers and ground substance.

d. Calcium salt ions (mostly Ca$^{2+}$ and PO$_4^{3-}$) then leave the blood through capillary walls and deposit (precipitate) out as rock-like calcium salt crystals, Ca$_3$(PO$_4$)$_2$, into the bony matrix.

1. This mineralizes the **Osteoid** and makes it hard as bone.
2. **Bony Matrix** = osteoid and calcium salt crystals.

d. Osteoblasts maintain the bony matrix to keep it strong.

e. Osteoblasts help to store extra calcium salts that come in with the diet on the surface of bone. This storage deposit of calcium salts can be broken down between meals by osteoclasts to maintain blood levels of calcium ions.

2. **Osteoclasts** (derived from monocytes) – breakd down the bony matrix to release Ca$^{2+}$

   a. live on the surface of bone along with osteoblasts.
   
   b. involved with bone resorption which is the breakdown of the bony matrix.

      1. Osteoclasts release enzymes (collagenase) that break down collagen fibers.
      2. They also release acids that solubilize calcium salts so that the ions enter the blood.
         Osteoclasts secrete H+ into IF using proton pumps (H+ AT pumps).

c. Osteoclasts help to release calcium ions from bone when blood calcium levels fall between meals.

**Calcitonin (CT)**

1. secreted by cells of thyroid gland.

2. Calcitonin is a peptide hormone (32 aa) secreted in response to high levels of circulating calcium. Once calcium levels are brought back to normal, CT release shuts off (NFL).

3. Actions of CT on Bone to bring calcium levels back into homeostatic balance.

   a. stimulates bone deposition: stimulate osteoblastic activity, thus promote surface deposition of calcium salts into the organic matrix secreted by osteoblasts.
      1. Osteoblasts are cells that live on the surface of bone.
      2. Osteoblasts take Ca$^{2+}$ and PO$_4^{3-}$ out of blood plasma and use them to build bone by laying down calcium phosphate in the bony matrix (Ca$_3$(PO$_4$)$_2$).
      3. The laying down of bony matrix (building up the density of bone) by osteoblasts is called bone deposition.

   b. inhibits bone resorption: primary effect is to inhibit the activity of osteoclasts, thus decrease bone resorption (CT antagonizes PTH’s effect).
      1. Osteoclasts are cells that live on the surface of bone.
      2. They are derived from macrophages (tissue monocytes).
      3. Osteoclasts secrete enzymes and acids that breakdown the bony matrix which releases Ca$^{2+}$ into blood plasma (releases phosphate ions as well).
      4. The breakdown of bone by osteoclasts is called bone resorption.
      5. Bone resorption decreases the thickness and strength of bone.
      6. Bone deposition increases the thickness and strength of bone.

c. CT only affects bone. It has no effect on the kidneys.
Parathyroid Gland

1. **PTH** is a **peptide** hormone (84 aa) secreted by the **parathyroid gland** (in **neck** beside thyroid gland)

2. hypercalcemic hormone that acts to raise [Ca2+] in **plasma** (hence the IF as well) between meals when it starts to fall too low
   a. makes sure that Ca2+ are available for cell use
   b. Ca2+ are continuously being lost from plasma as they move into cells and are lost in the urine
   c. Ca2+ always have a tendency to drop between meals
   d. this tendency must be countered to maintain Ca2+ homeostasis

3. **Effects of PTH on Bone**
   a. stimulates bone cells called **osteoclasts** to break down calcium phosphate crystals in the **bony matrix** to Ca2+ and Pi (inorganic phosphate, PO₄³⁻). Osteoclasts don’t have PTH receptors. PTH triggers the release of a growth factor that increases the number of osteoclasts, hence the rate at which they resorb the bony matrix
      1. Ca2+ and Pi ions then move into **blood plasma**
      2. the **bony matrix** serves as a huge reservoir of Ca2+ and Pi in the body
3. **osteoclasts** live on the **outer and inner surfaces** of bone in membranes called the **periosteum** (outer covering of bone) and the **endosteum** (covers inner surfaces)

4. **osteoclasts** release **enzymes** (e.g., collagenase) and **acids** (HCl) that **break down** the **osteoid** (organic part of bony matrix) and **dissolve away the calcium salt crystals** so that the resultant ions (Ca$^{2+}$ and Pi) enter plasma

5. the breakdown of bony matrix by osteoclasts is called **bone resorption**

6. **osteoclasts** are **white blood cells derived from macrophages**

b. **inhibits the activity of osteoblasts** (bone forming cells) that lay down the bony matrix

1. **bone deposition by osteoblasts builds up the bony matrix** – this occurs as bones replace “old” bone or increase the diameter of the bone to strengthen it in response to exercise

2. **osteoblasts (and osteoclasts) live on the surfaces of bone**

3. osteoblasts are derived from stromal cells, a type of connective tissue cell

4. **osteoblasts become osteocytes** when they are entrapped within lacunae

4. **Effects of PTH on the Kidney**
   a. **PTH decreases the amount of Ca$^{2+}$ that is found in urine**, thus preventing the loss of Ca$^{2+}$ in urine
      1. this effect of **PTH on the kidney helps to conserve Ca$^{2+}$ in blood plasma** by preventing its loss in urine (**PTH increases Ca$^{2+}$ reabsorption** in the PCT)
      2. it would be **counterproductive to increase Ca$^{2+}$ in blood if Ca$^{2+}$ were then lost in the urine**
      3. **PTH increases Ca$^{2+}$ reabsorption**
   b. **PTH increases the amount of Pi that ends up in urine**, hence decreasing the [Pi] in blood plasma (**PTH decreases Pi reabsorption so more Pi ends up in the urine and lost from the body**)
      1. **PTH increases Pi levels by stimulating osteoclasts to dissolve calcium salts** in the bony matrix which releases both Ca$^{2+}$ and Pi into the blood
      2. **PTH prevents an increase in Pi in blood plasma by increasing the amount of Pi that are incorporated into urine and excreted out of the body**
      3. **PTH decreases Pi reabsorption from kidney tubules**

5. **Regulation of PTH release**
   a. **involves a NFB loop** between free Ca$^{2+}$ in the blood and the cells of the parathyroid gland
   b. **falling levels of free Ca$^{2+}$ in plasma between meals stimulates the release of PTH**
   c. **rising levels of free Ca$^{2+}$ in plasma act back negatively on the parathyroid gland to shut off PTH release**
   d. PTH is the main hormone that **regulates the concentrations of Ca$^{2+}$ and Pi in blood plasma**
Homeostasis
1. **Homeostasis** is the maintenance of a relatively **constant internal environment** in the body
2. **Physiological mechanisms** help to maintain homeostasis
3. **Negative Feedback Loops** (NFL)
   a. homeostatic mechanisms to **control the release of a hormone** from glandular cells
   b. **during NFL**, rising concentrations of a hormone **inhibit its own secretion**

Pathologies Associated with PTH
1. **Hyperparathyroidism**
   a. **hypersecretion** of PTH by the parathyroid gland
   b. results in **chronically high levels of Ca2+** in the blood
   c. **effects of too much PTH**
      1. **excessive breakdown of bony matrix** and the “thinning” of bone – bone becomes brittle and more likely to fracture (osteoporosis)
      2. **excess Ca2+ in the kidney** can lead to the formation of **kidney stones** in the renal pelvis and in the ureters that damage the kidney over time. Kidney stones can be made of calcium salts (e.g., calcium oxalate). Kidney stones are rock like crystals that can be like pebbles. They block the flow of urine from the kidney to the urinary bladder
      3. **difficult contracting skeletal muscle** resulting in muscle weakness
2. **Hypoparathyroidism**
   a. **too little PTH** which leads to **lower than normal calcium levels in plasma** (hypocalcemia)
   b. **symptoms (same as hypocalcemia)**
      1. **muscle twitching** and muscle cramps (uncontrollable skeletal muscle contractions)
      2. **tetany of the diaphragm** that makes it hard to breather
Vitamin D (cholecalciferol) (sunshine vitamin)

1. Vitamin D
   a. is a steroid hormone made by epidermal cells (keratinocytes) of skin when exposed to UV light
   b. also called cholecalciferol
   c. Vitamin D3 is produced photochemically from 7-dehydrocholesterol in the skin of most vertebrate animals, including humans

2. Vit D is essential for the absorption of Ca2+ from the small intestine

3. 2 sources of vitamin D
   a. Vitamin D (cholecalciferol) production by skin cells (the skin is an endocrine gland).
      1. Cholesterol is acted upon by the UV wavelengths in sunlight and converted to cholecalciferol (Vit D)
      2. adequate amounts of Vit D can be made by the skin with only 10 min of sun/day to face, hands and neck (around 1 hour/wk)
   b. Vitamin D
      1. comes in with the diet
      2. fish, milk (Vit D added), eggs, cheese, cereal (Vit D added), orange juice (Vit D added)

4. Vitamin D is biologically inactive when it comes in with the diet or is made by skin cells
   a. Vitamin D must be converted by enzymes associated with liver and kidney cells to calcitriol
   b. calcitriol (made mostly by the kidney) is the biologically active form of Vitamin D in the body
      1. calcitriol is lipid soluble
      2. it diffuses into the cells and binds to receptors
      3. once bound to a receptor, it binds to the DNA and activates gene transcription
4. **Effects of Calcitriol** (one might also say the effects of vitamin D)
   a. *increase the absorption of Ca2+ in food* through ion channels in the epithelial cells that line the small intestine
      1. calcitriol *stimulates the activity of ATP-dependent active transport Ca2+ pumps* in the basolateral *membranes* of epithelial cells that line the small intestine
      2. calcitriol *stimulates the formation of a Ca+ binding protein called calbindin* which binds to and *carries Ca2+ rapidly through the cytoplasm* from the luminal side of the cell to the basal side. The transport of Ca2+ across the enterocyte cytoplasm is a *rate-limiting step for calcium absorption* from the intestine since it keeps the calcium concentration in the cell relatively low
   b. the *majority of Ca2+ that come in with the diet are not absorbed* and they end up in the feces
   c. calcitriol makes sure that some of the Ca2+ are absorbed from the lumen of the small intestine through the epithelial cells that line the SI and into the blood
   d. calcitriol also increases the *absorption of phosphate ions* (Pi, PO4^3-) from the intestine
Adrenal Gland
1. glands that sit on top of the kidneys; embedded in fat; the adrenal gland is formed by the merger of 2 fetal glands with different origins and functions.
2. two parts to the gland
   a. cortex (80% of total mass)– outer portion; adrenal cortex – secretes steroid hormones made from cholesterol
      1. mineralocorticoids – mainly aldosterone (discuss later with urinary system)
      2. glucocorticoids – cortisol and corticosterone (regulate blood sugar levels)
      3. sex steroids – DHEA (dihydroepiandrosterone), estrogens
   b. medulla (20%) - inner part – neurosecretory cells that secretes the neurohormone epinephrine and some NEpi (90% Epi and 10% NorEpi)) into the blood when the sympathetic NS turns “on” in response to stress
3. Mechanism of Action
   a. each of the adrenocortical steroid hormones binds with a receptor in the cytoplasm of the target cells
      1. the hormone-receptor complex then goes through nuclear pores into the nucleus and binds to a complementary hormone-response element in DNA (promoter site for gene)
2. binding starts **gene transcription** leading to the synthesis of new proteins (mostly **enzymes**) that carry out the effects of the hormone
b. epinephrine binds to membrane receptors (GPCR) and activates cAMP production which then acts as an intracellular second messenger that carries out the hormone’s effects on the cell

**Epinephrine from Adrenal Medulla**

1. **Regulation of Release**
   a. Secreted in response to **physiological** (cold, low blood glucose, **exercise**, tissue damage, surgery) and **psychological** (fear, guilt, anxiety) **stressors**.
   b. **Exercise** or **fear**, for example, will stimulate the adrenal gland to **release epinephrine** into the bloodstream.
   c. Epinephrine's dramatic effects start to take place within a **minute**.
   d. Collectively, these effects are referred to as the **Fight or Flight Response** or the **Emergency Response System** in that they help the individual meet an emergency situation. Hopefully, the situation will resolve itself relatively quickly so that the effects of epinephrine will not persist as is the case with chronic psychological stress. The effects are also called the **Stress Response System** or the **General Adaptation Syndrome** (GAS)
   e. **Exercise is the major stimulus for the release of Epi**. Exercise is the most common stressor to the body under normal conditions

2. **Actions of Epinephrine** (response occurs within 30 seconds of stress)
   a. **Cardiovascular**
      1. **Increase heart rate** (from 70 bpm to 180 bpm), increase **stroke volume** (70 to 140 ml), and **raise blood pressure** (120/80 to (160 to 220)/(80-100)
      2. **decrease blood flow** (vasoconstriction) to the **kidney** and digestive organs so that more is available to flow through skeletal muscle.
         a. Epinephrine acts to constrict the smooth muscle within the arteriolar wall, thus **vasoconstricting** blood vessels that supply the visceral organs.
         b. Epinephrine vasodilates arterioles in skeletal muscle.
         c. vasodilation to exercising skeletal muscle occurs primarily by autoregulation. Localized increases in CO2, H+ and lactic acid that accompany skeletal muscle contraction during exercise relax smooth muscle in the walls of arterioles (vasodilate). These chemicals also relax precapillary sphincter muscles which opens up capillary beds
   b. **Bronchiodilation** in the lungs: Dilate respiratory or bronchiolar tubes (bronchiodilation) so as to increase the amount of air that can move into and out of the lung with each breath. This increases the availability of oxygen. Epinephrine acts to **relax** the smooth muscle around the bronchioles allowing the tubes to expand.
   c. **Increase hepatic Glycogenolysis to Raise blood glucose levels**: Stimulate hepatic glycogenolysis which increases blood sugar levels for use as a fuel substrate to make ATP. Some of the excess glucose in the diet is taken up by liver cells and used to build glycogen (glycogenesis). This glycogen is then available for glycogenolysis.
d. **Increase lipolysis** - Increase **lipolysis** in adipocytes to provide fatty acids and glycerol as fuel substrates for ATP production.

e. **decrease digestion** – decrease **peristalsis, decr blood flow** to intestinal wall, decr glandular secretions

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**Cortisol (hydrocortisone) from Adrenal Cortex**

1. Secreted by the adrenal cortex (**corticosteroid**)
2. **Regulation of Release**: Like epinephrine, cortisol is released from the adrenal gland when the body is subjected to **physiological and psychological stressors**.
3. **Major Hyperglycemic Agent**
   a. Cortisol is an **important hyperglycemic agent** - acts to **raise blood** sugar levels when they are **lower** than **normal** (**between meals** or when one is in a fasting state).
b. It is **critical** to maintain homeostatic concentrations of **glucose** in the blood for use by brain neurons regardless of whether one has eaten for days or even weeks (fasting state).

c. The liver can supply glucose to the blood from **glycogenolysis for 8-12 hours** (if don’t exercise). **If exercise, then 2-6 hours** depending on the type of exercise (e.g., about 3-4 hours in long distance cycling or marathon). Once glycogenolysis has paid out this glucose, the body must begin to produce glucose by a process known as **gluconeogenesis**.

4. **Major Effects of Cortisol**
   
a. **Stimulate hepatic gluconeogenesis (GNG)**
      1. **Gluconeogenesis** is the conversion of non-carbohydrate compounds like amino acids, lactate, pyruvate, and glycerol to glucose. Fatty acids cannot be converted to glucose.
      2. The pathway is most active in **liver** cells.
      3. This **ATP-dependent** process occurs **between meals** when the body isn’t digesting food and when glycogen reserves have been exhausted.
      4. The body must **always maintain** adequate amounts of **glucose** in the blood for use by brain neurons, hence glucose is synthesized by **gluconeogenesis**.
      5. Even in the absence of eating, gluconeogenesis can continue to **supply glucose** in the fasting state until one **dies** of starvation.
      6. This is cortisol's **major effect** in the body.
      7. **Cortisol** stimulates the synthesis of **hepatic enzymes** that promote **gluconeogenesis**.
      8. During **prolonged fasting** and **exercise**, **gluconeogenesis** in the liver using amino acids from muscles may be the only source of blood glucose.

b. **Increase Proteolysis**
   1. **Stimulates protein catabolism** (actin and myosin of myofilaments) **in skeletal muscle cells** and connective tissues.
      a. Cortisol will induce a condition known as "**muscle wasting.**"
      b. Cortisol stimulates the breakdown of protein in skeletal muscle cells to supply the amino acids for **gluconeogenesis**.
   2. cortisol inhibits protein synthesis in liver cells and within white blood cells. This can result in a decrease in the production of liver proteins (e.g., albumin, prothrombin, fibrinogen) and a decrease in the production of antibodies that can make the body more vulnerable to infection.

c. **Stimulates lipolysis in adipocytes** - Cortisol increases the release of fatty acids and glycerol from adipocytes for use as a fuel substrate, thus "saving" glucose for use by brain cells. FA’s are carried bound to albumin in the blood. Glycerol is usually taken up by liver cells and converted to glucose by glycolysis.
   1. Starvation usually results in death soon after the fat cells run out of fat.
   2. when the body runs out of stored glucose and fat, then it must rely almost exclusively on the breakdown of protein for energy and there is a rapid wasting away of muscle and connective tissues.
   3. death results from heart failure, kidney failure, or infection
5. **Control of cortisol secretion**
   a. CRH from the hypothalamus stimulates the release of ACTH from the AP
   b. ACTH stimulates the release of cortisol from the medulla of the adrenal gland
   c. cortisol will feedback in a negative way to suppress the release of CRH and ACTH, thus regulating its own levels in plasma

**Anti-inflammatory and Immunosuppressive effects of cortisol**
1. *inflammation* is the response of the body to tissue damage
2. cortisol suppresses the inflammatory response so it doesn’t harm the body
3. **effects of cortisol**
   a. suppresses the migration of neutrophils to site of injury
   b. inhibits the phagocytic activity of macrophages and neutrophils
   c. inhibits the production of antibodies by lymphocytes
4. Administering large doses of cortisol can reduce the pain and swelling associated with inflammation

**Aldosterone from Adrenal Cortex**
1. secreted by adrenal cortex (corticosteroid)
2. *increase Na*⁺ *reabsorption* from filtrate within the kidney (less Na⁺ in urine); increase Cl⁻ reabsorption; increase salt (NaCl) reabsorption
3. *increase water reabsorption* (less urine volume)
4. *increase K*⁺ *secretion* (more K⁺ in urine)
5. *Decreases in aldosterone* can lead to dehydration and electrolyte imbalance because of excess urine production, salt loss, and high blood levels of potassium ions – death in several days
<table>
<thead>
<tr>
<th>Hormone</th>
<th>Pathway</th>
<th>Effect</th>
<th>Chronic Effect</th>
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<tbody>
<tr>
<td><strong>Cortisol</strong></td>
<td>gluconeogenesis</td>
<td>increase blood glucose</td>
<td>elevated glucose, can lead to cataracts</td>
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<td></td>
<td>protein catabolism</td>
<td>increase amino acids in plasma</td>
<td>muscle wasting and bone degradation</td>
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<td></td>
<td>lipolysis</td>
<td>increase fatty acids in the blood</td>
<td>lower pH of blood (acidosis), feel nauseous and sick, tired, contributes to formation of ketone bodies in plasma (fatty acids in excess break down to acids called ketone bodies)</td>
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<td></td>
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<td>suppress white cell activity</td>
<td>increase susceptibility to disease (get sick more often (flu, cold...)</td>
</tr>
<tr>
<td><strong>Epinephrine</strong></td>
<td>liver glycogenolysis</td>
<td>increase glucose in the blood</td>
<td>elevated glucose</td>
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<td></td>
<td>cardiovascular</td>
<td>increase heart rate and blood pressure</td>
<td>Hypertension, restlessness, difficulty sleeping</td>
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<td></td>
<td></td>
<td>redistribute blood away from visceral organs and to skeletal muscle</td>
<td>digestive problems</td>
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<tr>
<td></td>
<td>respiratory</td>
<td>increase diameter of respiratory tubes</td>
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<td></td>
<td>iris smooth muscle</td>
<td>dilate pupils</td>
<td>Indicator of guilt if lying</td>
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Pancreas - located beneath the stomach in the abdominal cavity. The pancreas has a dual function: (1) produces and secretes a pancreatic fluid that flows into the small intestine and aids in digestion, and (2) produces and releases two antagonistic glucose-regulating hormones: glucagon and insulin. INS and GCG are the primary hormones that regulate blood glucose levels. The pancreas is both an endocrine and an exocrine gland.

1. **Structure of the Pancreas**
   a. **Acinar cells** and **duct cells** make up over 98% of the pancreatic mass
      1. **acinar cells** secrete the enzyme-rich portion of the pancreatic juice
      2. **duct cells** secrete the alkaline NaHCO3 portion of the pancreatic juice that aids in digestion.
      3. Since the pancreatic juice flows into ducts that open into the lumen of an internal tube (small intestine) the pancreas is an exocrine organ.

   b. **Islets of Langerhans (pancreatic islets)**
      1. There are roughly 1-2 million islets in the pancreas, but they still only make up about 2% of the pancreas.
      2. Scattered among the acinar cells of the pancreas are clusters of hormone-secreting cells called islets of Langerhans.
      3. The islet cells produce mostly insulin (β or beta cells, 70% of total) and glucagon (α or alpha cells, 20%). Since the pancreas secretes hormones it is an endocrine gland. Delta cells secrete GHIH and F cells secrete pancreatic polypeptide.
2. **Glucagon (GCG)** - hyperglycemic agent (raise blood sugar levels; glucose is sometimes called blood sugar and marketed as dextrose). One molecule of glucagon, for example, can stimulate the release of one million glucose molecules into the blood.

   a. **Regulation of Glucagon Release:** (1) Glucagon is released when blood glucose levels are too low (between meals). (2) It acts to bring blood sugar levels back to normal. Once glucose levels rise to normal levels, glucagon secretion stops. (3) It is critical to maintain glucose homeostasis, because of the critical need of neurons for glucose. If neurons do not receive a steady supply of glucose via the blood stream they malfunction which can result in disorientation, convulsions, and coma.

   b. **Glucagon** stimulates two important chemical pathways involved with glucose homeostasis

      1. **Hepatic (hepatic means liver) glycogenolysis between meals until liver glycogen runs out**
         a. breakdown of stored glycogen in the liver to pay glucose out into the circulation.
            1. liver can store around 100 gm of glucose as glycogen.
            2. Stored glycogen can provide 8-12 hours of glucose (2-6 hrs if exercise) by hepatic glycogenolysis
            2. excess carbohydrate coming in with a meal is taken to the liver and stored as glycogen
         b. Only the liver can use its stored glycogen as a source of additional blood glucose.
            1. There are approximately 100 grams of glucose stored in the liver, hence the supply is finite.
            2. The glucose that is derived from the breakdown of glycogen in muscle is used by glycolysis within the muscle cells themselves for ATP production.
            3. Skeletal muscle holds about 400 grams of glycogen.

            | Glycogen source | gms | lb  |
            |-----------------|-----|-----|
            | Liver           | 100 | 0.22|
            | Skeletal muscle | 400 | 0.88|

   c. During a meal, glucose is absorbed and when in excess of body needs is used to replenish glycogen reserves in liver and muscle cells (glycogenesis).

   d. Once these stores are full, the excess glucose is taken up by fat cells and shunted down biochemical pathways that lead to the production of fat molecules (triglycerides).

   e. glycogenolysis and gluconeogenesis produce G-6-P from glycogen

   f. **Glucose 6-phosphatase** (G6Pase)
      1. enzyme that hydrolyzes glucose-6-phosphate to a phosphate group and free glucose.
      2. Glucose is then exported from the cell via glucose transporter membrane proteins (GLUT).
3. The formation of glucose is the final step in gluconeogenesis and glycogenolysis and therefore plays a key role in the homeostatic regulation of blood glucose levels.

4. This enzyme is found in liver cells, but not in muscle cells.

5. Since muscle cells lack G6Pase, the glycogen that muscles store is not usually available for the rest of the body's cells because the glucose-6-phosphate they form from glycolysis cannot cross the sarcolemma unless it is dephosphorylated.

2. **Hepatic gluconeogenesis** - when glucose levels are low, liver cells will take in amino acids and other non-carbohydrate molecules and convert them to glucose. Once formed, glucose enters the circulation to maintain blood glucose levels. This process is often accompanied by a breakdown of skeletal muscle which serves as the source of the amino acids as proteins are catabolized.

3. **Stimulates Lipolysis** - Glucagon stimulates a lipase enzyme in adipose cells to catalyze the hydrolysis of stored triglycerides which results in the release of fatty acids (and glycerol) into the bloodstream. Fatty acids are then taken up by cells and broken down to acetate for use by the mitochondria in the production of ATP (e.g. resting skeletal muscle, the liver, and other organs, use primarily fatty acids as a fuel substrate).
3. **Insulin** (INS) - Insulin is a hormone that promotes many biochemical pathways that help with growth and the processing of digested nutrients, especially glucose and fats. It is an anabolic hormone in that it stimulates processes that synthesize large molecules from smaller ones. Insulin is released during or after a meal when nutrients (especially glucose) are plentiful.

   a. **Major Target Organs**: Insulin's major effects are on connective (mostly adipose) and muscle tissues. Insulin also stimulates the formation of glycogen in the liver. Some cells of the body do not depend on insulin for glucose uptake (kidneys, brain, liver, and red blood cells)

   b. **Regulation of Insulin Release**: The primary regulator is rising plasma levels of glucose, but rising levels of amino acids and fatty acids will also trigger the release of insulin. Circulating levels of these nutrients are most likely to be high while one is digesting a meal. Conversely, falling levels of glucose (and other nutrients) suppress insulin release.

   c. **Metabolic Actions**: Insulin is a powerful anabolic hormone

      1. **CARBOHYDRATE**: Major hypoglycemic agent (bring glucose levels down) - Insulin is the most important hormone that acts to decrease blood sugar levels when they rise too high during digestion of a meal. Circulating insulin lowers blood glucose by
a. Increasing the transport of glucose into muscle and adipose tissue by facilitated diffusion (about 60% of the body's cells; most significant effect on skeletal muscle cells)
b. Activates the enzymes of glycogenesis in liver and muscle cells (and inhibits glycogenolysis)

2. **PROTEIN**: Promotes amino acid uptake and protein synthesis in muscle cells. Insulin is essential for normal growth and repair processes.

3. **LIPID**: Promotes lipogenesis or the synthesis of triglycerides in adipocytes and the liver. Thus insulin promotes fat storage, in part by shunting glucose into adipocytes where it can be converted to fat. FA's taken up by liver are converted to TG's, bonded to VLDL's and transported to adipocytes by way of blood.

d. **Regulation of Glucose Homeostasis** - It is critical that brain neurons have a steady and dependable supply of glucose for use as a fuel substrate to make the huge amounts of ATP necessary to sustain their base-level activity. Most cells of the body (e.g. muscle cells) when at rest use mostly fatty acids as a fuel substrate. Neurons cannot do this. They must oxidize glucose.

1. **Hypoglycemic Agent**: Insulin is the only hormone that acts to lower blood sugar levels while digesting a meal when glucose is too high. Without an insulin effect, blood sugar levels remain high and the symptoms of diabetes appear.

2. **Hyperglycemic Agents**: Cortisol and glucagon (and GH, epinephrine, thyroxine) act mostly between meals and during exercise to raise blood sugar levels. Without these hyperglycemic agents, blood sugar levels would remain too low and cause dizziness, muscle fatigue, mental confusion, convulsions, and even unconsciousness, coma, and death.
Hormones that Control Nutrient Metabolism

1. **Glucose** metabolism (major effects on the liver)
   a. hepatic glycogenesis – insulin
   b. hepatic glycogenolysis – glucagon, epi, cortisol
   c. hepatic gluconeogenesis – cortisol, glucagon

2. **Protein** (major effect in skeletal muscle)
   a. protein synthesis – insulin, GH, thyroxine, estrogen, testosterone
   b. proteolysis – cortisol

3. **Lipid** (major effect in adipocytes)
   a. lipogenesis – insulin
   b. lipolysis – GH, cortisol, glucagon, epi, thyroid hormone

Calcium Regulation

1. **Calcitonin**: Hypoglycemic agent that decreases calcium in the blood by stimulating osteoblasts
2. **PTH**: hyperglycemic agent that increases calcium in the blood by stimulating osteoclasts

Water reabsorption (results in less urine volume)

1. **ADH, Aldosterone**: decrease urine volume by increase water reabsorption from the kidneys

Pineal Gland

1. Located on the roof of the III ventricle of the brain diencephalon
2. produces melatonin at night
3. melatonin helps to maintain one’s mood and regulate sleep-wake cycles (diurnal rhythm)
TABLE 7-4 Summary of Reactions in Fuel Metabolism

<table>
<thead>
<tr>
<th>Metabolic Process</th>
<th>Reaction</th>
<th>Consequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glycogenogenesis</td>
<td>Glucose → glycogen</td>
<td>↓ Blood glucose</td>
</tr>
<tr>
<td>Glycogenolysis</td>
<td>Glycogen → glucose</td>
<td>↑ Blood glucose</td>
</tr>
<tr>
<td>Gluconeogenesis</td>
<td>Amino acids → glucose</td>
<td>↑ Blood glucose</td>
</tr>
<tr>
<td>Protein Synthesis</td>
<td>Amino acids → protein</td>
<td>↓ Blood amino acids</td>
</tr>
<tr>
<td>Protein Degradation</td>
<td>Protein → amino acids</td>
<td>↑ Blood amino acids</td>
</tr>
<tr>
<td>Fat Synthesis (Lipogenesis or Triglyceride Synthesis)</td>
<td>Fatty acids and glycerol → triglycerides</td>
<td>↓ Blood fatty acids</td>
</tr>
<tr>
<td>Fat Breakdown (Lipolysis or Triglyceride Degradation)</td>
<td>Triglycerides → fatty acids and glycerol</td>
<td>↑ Blood fatty acids</td>
</tr>
</tbody>
</table>

Overview of reactions in fuel metabolism

Summary of major pathways involving organic nutrients
Nutrients are stored for use between meals

1. **excess glucose** that comes in with the diet is taken up and stored as glycogen in the liver, glial cells in CNS, muscle, and fat cells (adipocytes).
   a. Glycogen is a polymer of glucose.
   b. A glycogen molecule may contain up to **120,000 glucose molecules** bonded together in a branched chain.

2. Once the liver and muscle cells are full of glycogen (glucose-storage polymer), additional glucose goes into fat cells and gets converted to fatty acids and glycerol to make triglycerides (TG, fat molecules).

3. **excess amino acids** are used first for protein synthesis (mostly enzymes and structural proteins within cells). Once the **protein needs of the cells are met**, the excess amino acids are converted by cells to glucose and fatty acids. The fatty acids end up being stored in fat cells as TG’s.

4. **major site for energy storage is fat tissue** (adipocytes)

5. **Lipids are the preferred storage molecule** since they take up much less space than glycogen
   a. Lipids stick together into a tightly compacted clump in the cytoplasm (fat droplet) with no water molecules
   b. Glycogen is hydrophilic and attracts water molecules that H-bond to it. The water molecules take up space and add mass to a cell
   c. Lipids contain a lot of high energy C-H bonds that can be used during mitochondrial stages of cellular respiration to make NADH (fatty acids broken down to acetate which then enters Krebs cycle)

7. A lot of energy is stored in the amino acids of structural proteins, primarily muscle mass

**Brain depends solely on glucose**

1. Brain neurons only use glucose to make ATP by cellular respiration. Most cells can use amino acids and fatty acids in addition to glucose
2. Blood glucose concentration (humans): **70-110 mg/100 mL of plasma** (80-90 mg/dL, 80-90 mg%)
b. the byproducts of digestion include **amino acids**, **simple sugars** like **glucose** and **fructose**, and **fatty acids**.

c. These compounds are then **absorbed** through the cells that **line the intestine** into the **blood**

d. **extra nutrients** that are **absorbed** are stored as glycogen and TG’s

e. **nutrients** are in excess of what cells need
   1. hepatic and muscle **glycogenesis**
   2. **protein synthesis**
   3. **lipogenesis in adipocytes** (TG synthesis from fatty acids and glycerol)

f. main **hormone** that stimulates **biochemical pathways** that process excess nutrients: **insulin** (anabolic)

2. **Postabsorptive State** (fasting state)
   a. the **average meal** is completely digested and absorbed in about **4 hours**
   b. if one **eats 3 meals a day at 7, 12 and 6**, then no nutrients are being absorbed during the **late morning, late afternoon and across the night**
   c. these times are the **postabsorptive periods** when one is in a **fasting state**
   d. **during the fasting state**, the following occur to supply glucose into the blood for cells to use, especially brain neurons
   1. **hepatic glycogenolysis** – breakdown liver glycogen to glucose
      a. the liver **stores about 8-12 hours of glucose as glycogen**
      b. as a result, the **hepatic glycogenolysis** between meals can **supply glucose** to the blood for about 8–12 hours in the post-absorptive state **before gluconeogenesis** kicks in
      c. glucose derived from liver glycogen will be the **primary source of blood glucose** to be used by the rest of the body for fuel.
      d. **when the liver runs out of glycogen**, then the body turns to **gluconeogenesis**
      e. **only the glycogen stored in the liver can be used to maintain blood glucose levels**. The breakdown of glycogen in muscle supplies glucose that is used exclusively in muscle cells.
      f. main hormones that stimulate hepatic glycogenolysis: glucagon, epinephrine

2. **hepatic gluconeogenesis**
   a. conversion of mostly **amino acids in the liver to glucose**
   b. **Proteolysis** in muscle occurs at the same time to provide **amino acids** to the liver for gluconeogenesis.
      1. This is an **undesirable** effect of gluconeogenesis
      2. over time, gluconeogenesis and the breakdown of protein to supply amino acids will lead to muscle “wasting”
   c. this biochemical pathway to generate glucose **starts once the liver has run out of stored glycogen**
   d. main hormones that stimulate gluconeogenesis: primarily cortisol, epinephrine

3. **Lipolysis** – TG’s broken down in adipocytes to supply FA’s into the blood for cell’s to use to make ATP. The glycerol produced usually goes into the blood to the liver where it is converted to glucose