Section Two: Chapter 12: The Endocrine System

Overview

In the body the **endocrine system**, together with the **nervous system**, is considered one the two long distance control systems of the body. In contrast to the nervous system, the endocrine system operates as a network of glands and organs that work together or independently to regulate body functions. In terms of etymology (word origin), the term 'endocrine' comes from endo = within, and crine = to secrete or separate; thus, it loosely means "secreting from within".

The Endocrine System works by releasing chemical messengers called **hormones** into the blood stream which are then transported throughout the body via the blood vessels. Hormones act on specific **target cells** that have **receptors** for the **specific signal molecule** (hormone) released. As such, a hormone can only affect cells or tissues that have receptors for it. When the hormone binds to the receptors on or within the target cell, it produces a response in the target cell. The locations of various endocrine glands throughout the body are shown in **Figure 12.1** below.

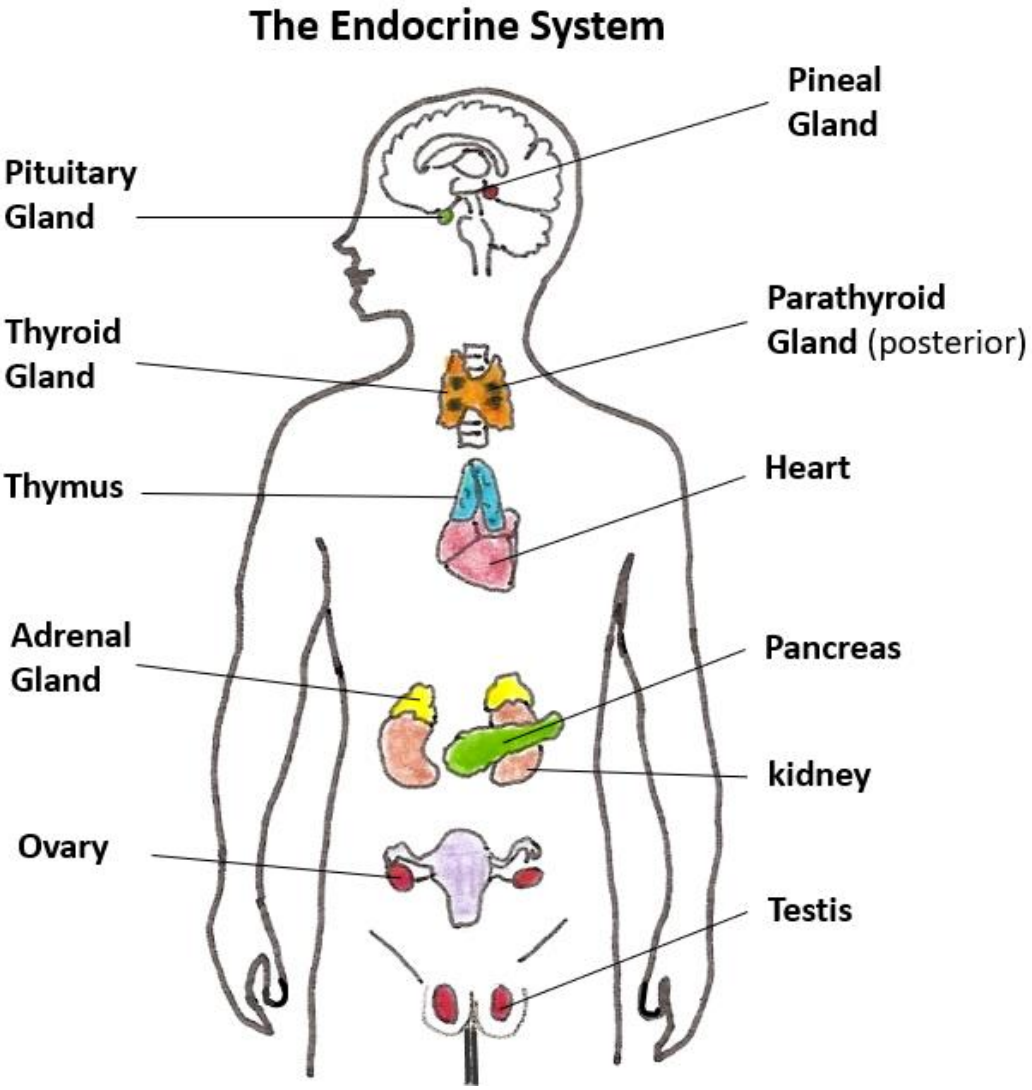


Figure 12.1 Shown in the drawing here are important primary and secondary endocrine glands. They are located throughout the body, including regions of the brain, cardiovascular, renal, digestive and reproductive systems.

The Nervous System versus the Endocrine System

Here below is a simple comparison between the **Nervous** and **Endocrine** systems.

The Nervous System conducts electrical signals throughout the body with neurons. **Neurotransmitters** are the chemical messengers released from neurons and they travel across a narrow cleft at the **effector tissue** and bind to receptors on the target cell, as seen below in **Fig. 12.2**. Communication is very fast, typically measured in milliseconds, it is brief and it is usually highly specific in terms of location.

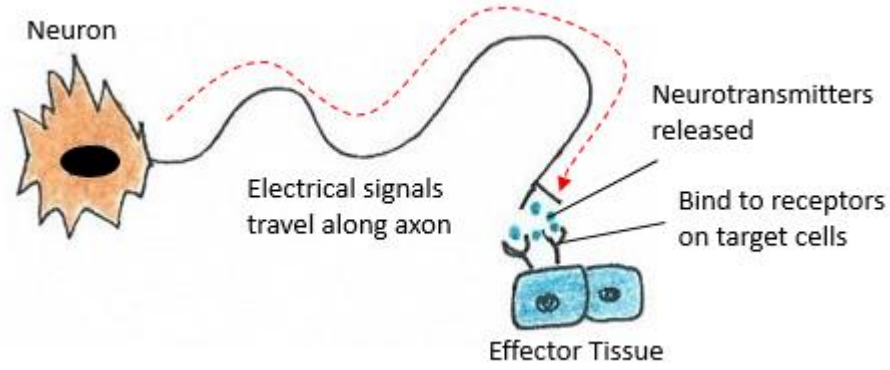


Figure 12.2 The neuron is the cell of communication in the nervous system and sends very fast electrical signals along its axon, which are converted to chemical signals with the release of neurotransmitters at the synaptic end bulb. This signal molecule binds to receptors on the surface of the target cells and changes the activity of the cell.

The Endocrine System, in contrast to the nervous system, conducts chemical signals throughout the body via glands. The chemical messengers released by these endocrine glands are called **hormones** and they travel through the blood stream to **target cells** that have receptors for those hormones, as seen below in **Fig. 12.3**. Communication can occur within seconds but this is considered slow compared to the nervous system. The signals often linger for a longer time and are usually more expansive in terms of effects on various tissues, meaning hormones often have a broader effect. Because hormones are in the bloodstream they can be delivered almost anywhere. The only way any tissue will respond to a hormone, neurotransmitters or any other substance, is if they have sufficient receptors for that signal.

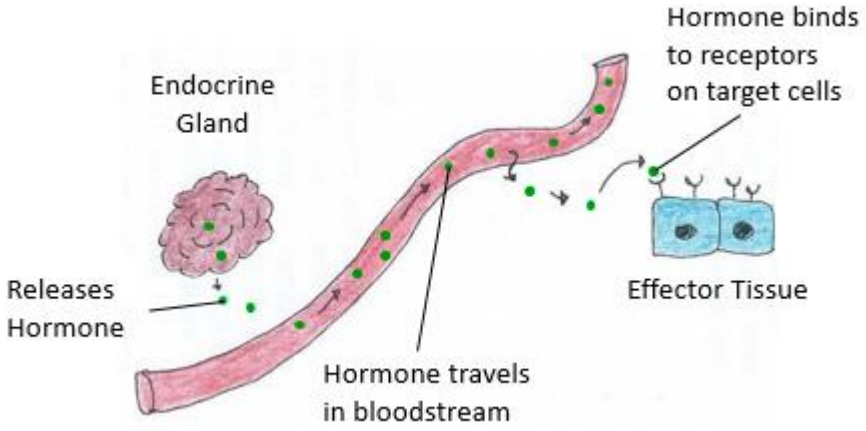


Figure 12.3 Endocrine glands release hormones which travel in the blood to the effector tissue, these are cells with receptors that bind these hormones, called the target cells for that specific hormone. The targets cell's activity can be changed in multiple ways as a result of the hormones actions.

The Timeframe of Hormone Actions

In contrast to the nervous system, the endocrine system is said to have a **slower** response to stimuli. It is not slow per se, but the actions of hormones are nowhere near the ***millisecond*** speeds involved with the nervous system. This is because hormones must be released from their glands into the blood stream first, and then flow throughout the body to reach their target tissue, and this takes more time.

An overall timeframe for hormone action is very broad, spanning an array of options. Some hormones can act within seconds, for example epinephrine or adrenaline. Others may act over a few minutes or hours, like insulin, glucagon or cortisol. Some may take weeks or months, like the sex hormones estrogen and testosterone. Or they may even have effects over many years, like human growth hormone and thyroxine.

Upregulation and Downregulation of Receptors

Cells of the body are thought to have receptors on their external surface (plasma membrane), as well as having internal receptors in the cytoplasm and nucleoplasm. Hormones circulating in the blood can bind to these receptors and change the activity of the cell.

It is worth mentioning again that receptor density anywhere on or within a cell can change. This will depend on the **intensity of the signal**. The familiar image seen in **Fig. 12.4** below shows how cell receptors can up-regulate (increase in number as in **a**), and therefore become more sensitive to the stimulus, due to a reduction or lack of exposure to the hormone or substance. In contrast, receptors can down-regulate (decrease in number as in **c**) for the same cell and become less sensitive to the stimulus. This could be caused by excessive exposure or over stimulation with the hormone or a substance.

a) Upregulation **b) In between** **c) Downregulation**

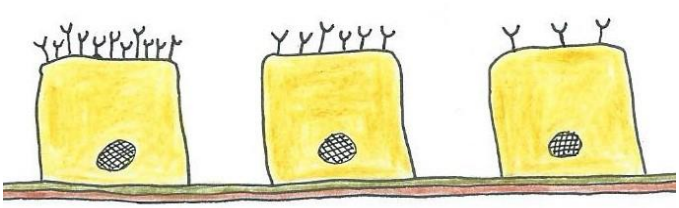


Figure 12.4 The number of receptors on the plasma membrane surface of cells can change, depending on the intensity of the signal. Cell receptors can up-regulate (increase in number) as seen in **a)** and they can down-regulate (decrease in number) as seen in **c)** and can also exist somewhere in between the two, as seen in **b)**.

Receptors on a cell are there to receive signals and allow the cell to respond. In relation to our discussion of hormones, the more receptors a cell has for that specific molecule, the more strongly the cell will respond to it. And vice versa; the fewer receptors a cell has for that specific molecule, the less strongly the cell will respond to it. the Thus a key element to the sensitivity of a target cell for any signal molecule is **receptor density**.

Upregulation of receptors is when the cell increases receptor density in response to a stimulus. **Downregulation** of receptors is when a cell decreases receptor density in response to a stimulus.

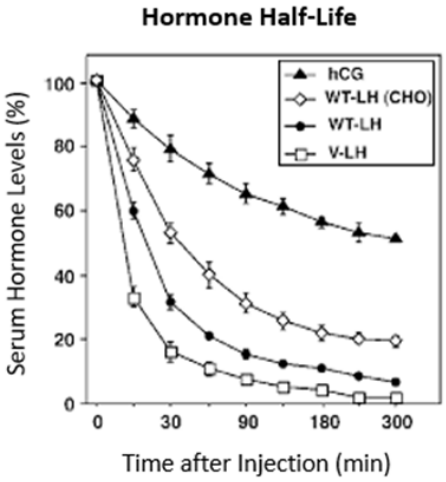
Downregulation of receptors occurs after chronic exposure to an excessive amount of a hormone. The consequence is that the cell becomes '**desensitized**' to that substance and will required a greater amount in order to evoke a similar response to the previous stimulus. On the contrary, the upregulation of receptors can '**super-sensitize**' cells. This can be seen after a prolonged absence of the hormone; when it is re-introduced there is an elevated sensitivity to even small amounts of it.

Stopping Hormone Actions After their Release

Much of this chapter is dedicated to how various hormones are released from endocrine glands in the body. Before going into those detailed discussions, let's quickly outline how hormones are stopped or turned off after they are released, so that their actions in the body are ended when appropriate.

It is necessary for the actions of hormones to be terminated once they have acted in order to maintain homeostasis. The most common way hormone actions are terminated are by **negative feedback loops**, by which the hormone (the end product) inhibits the enzyme at the start of the metabolic pathway that initiated the release of it. This is also known as **End Product Inhibition**, covered in Enzymes, Chapter 3.

Any residual hormones that remain in the bloodstream are usually **degraded by enzymes** into inactive metabolites, which are then **excreted in urine**. This is why testing urine for various substances (**urinalysis**) is a valuable method of detecting what metabolic activities the body has recently been engaged in, because hormones and their metabolites (products of their catabolic breakdown) will be eliminated in the urine as part of renal clearance.



Hormones and other signal molecules have a **half-life**, this is the time it takes for the hormone to lose half of its physiological activity. Hormones have different half-lives depending on their role, but in general, over time they lose their potency and become less and less affective as they are cleared from the bloodstream. Shown in the graph (left) are different hormone preparations in the bloodstream, where serum hormone levels were measured. Looking at the graph (left), all hormones levels decrease in the serum, predominantly as they are cleared from the blood by the **kidneys** of the **renal system** and excreted from the body.

Hormonal Rhythms of the Body

An important concept regarding hormones, and also regulation of the entire body, is the existence of various **rhythmic cycles** that are involved in hormone secretion. The three biological cycles discussed below are: Ultradian, Circadian and Infradian rhythms.

Ultradian rhythm: This is a biological activity having a period of recurrence shorter than a 24-hour day, but longer than an hour. For example, **adrenocorticotropic hormone** (ACTH) secretion has multiple small peaks during the day with an interval between them being less than 24 hours.

Circadian or diurnal rhythm: This is a natural biological activity or oscillation of an endogenous rhythm with a period of approximately 24 hours, that persists in the absence of external timing signals and repeats about every 24 hours. For example, **melatonin** regulates sleep-wake cycles in a classic circadian rhythm. **Cortisol** is a another hormone that is typically released like clockwork. Its circadian rhythm shows a rise in cortisol during the night when we are asleep, and a peak within the first hour after awakening.

The term **diurnal** is used when a circadian rhythm is associated with the light-dark cycle. The hormones melatonin and cortisol have contrary rhythms in the body, but also overlap. Melatonin release is naturally initiated by a decrease in light intensity when the sun sets and increases the drive to sleep. These levels peek at about 3am and then begin to quickly drop off to their low daytime levels at around 6am (see **Fig.**

12.5). Just as melatonin levels are directly correlated to sleep diurnal cycles, so too are the serum levels of cortisol. The cortisol levels begin their sharp upward rise at about 6am in the morning, hitting their peak at around 9am, diminishing to their low levels by about 12pm (see **Fig. 12.6**).

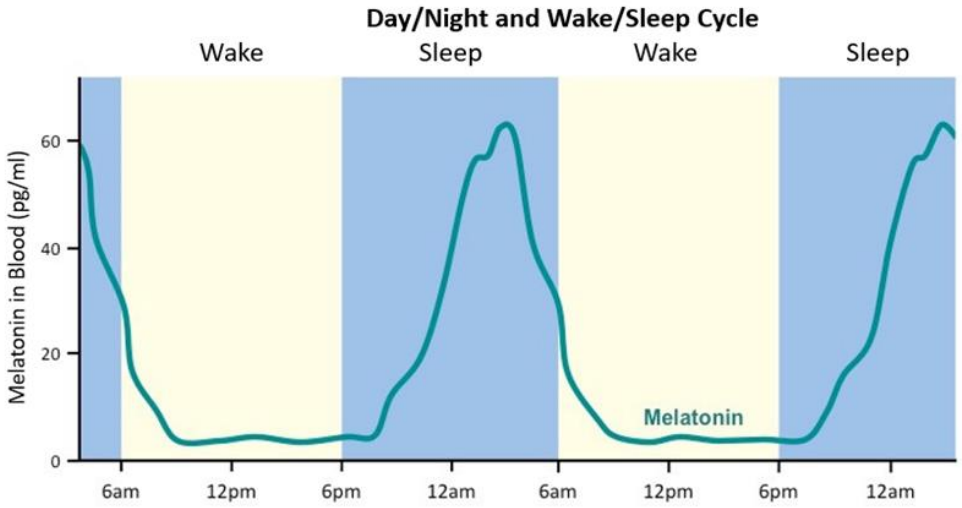


Figure 12.5 This graph shows the classic circadian rhythm of the Day/Night and Wake/Sleep cycle maintained predominantly by the hormone melatonin. There are low melatonin levels in the blood during the wake phase (day) and high levels during the night that promote sleep.

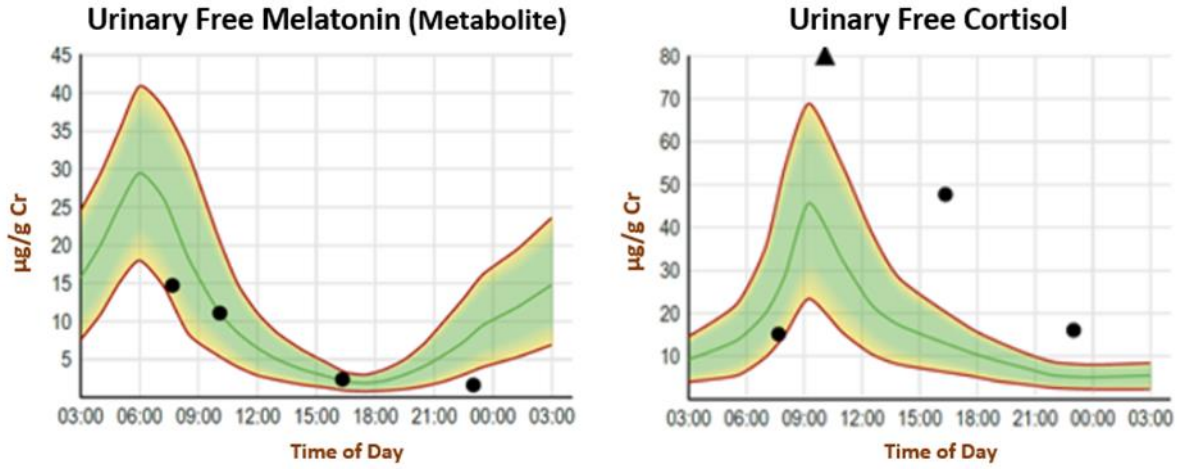


Figure 12.6 This graph shows the classic circadian rhythms of melatonin metabolites and cortisol levels in urine.

The hormone **cortisol** has important roles in metabolism, blood pressure and blood sugar regulation. Cortisol prepares the body for activity immediately upon waking, it is designed to make us alert and aware before consuming anything. As a clarification, the substance **cortisone** is a precursor to cortisol, and predominantly has anti-inflammatory properties. This is why cortisone drugs can be used medicinally by injecting it at sites of injury to reduce inflammation.

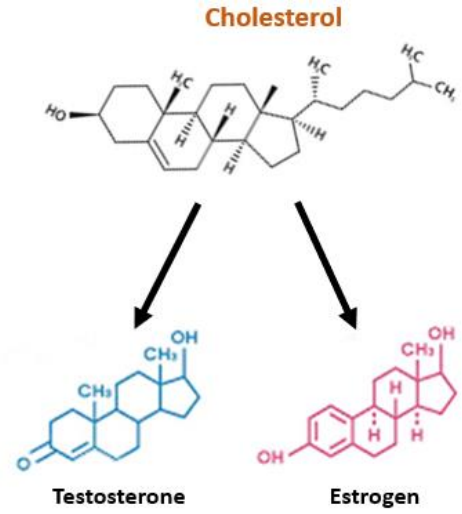
Linking back to half-lives and elimination of hormones in the urine, both melatonin and cortisol levels in the blood can be determined by their concentration in urine. In **Fig. 12.6** above, the melatonin metabolite MT6's and cortisol can be easily measured in urine to provide insight into the mechanisms that have an influence on circadian rhythms.

Infradian rhythm: This is a rhythm or cycle having a period of recurrence that is longer than a 24-hour day. That is, occurring less than once a day. For example, the steroidal **female sex hormones** regulate the menstrual cycle in females with a cyclic activity that usually range between 26-30 days in length. The cycle is recurring and in a predictable manner.

Classificaion of Hormones

There are a surprising number of ways that hormones in the human body can be classified. The central element for classification that is useful in physiology is by their **chemical structure**. There are two types of classifications using chemical structure discussed below: **A)** has **3** categories, and **B)** has **2** categories. It is helpful to be familiar with both of these classifications, as it provides insight into where various substances are derived from, and how this makes them similar to some signal molecules, and very different to other molecules.

A) The most common way is to categorize hormones based on their chemical structure by placing them in one of three categories: **Lipids**, **Peptides** and **Amines**.



1. Lipid soluble Hormones

These hormones are made by lipids, mostly by cholesterol and are not water soluble. The majority of lipid hormones are derived from **cholesterol**, which creates the powerful **steroid sex hormones** like **estrogen** in women and **testosterone** in men. **Cortisol** and **aldosterone** are two more important steroid lipid hormones, both are made by the adrenal cortex.

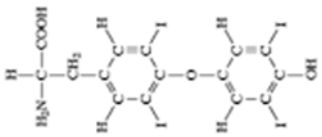
2. Peptide hormones

These hormones are made by short chains of amino acids that are typically called **polypeptides**. These are the most common type of hormone in the human body. Some familiar example include **oxytocin**, **antidiuretic hormone**, **insulin**, **glucagon**, **growth hormone**, **follicle-stimulating hormone** and **somatostatin**. In general, they are water soluble.

3. Amine Hormones

These hormones are derived from the amino acids **tyrosine** and **tryptophan**. Many of these hormones have an -**ine** ending of their name, for example epinephrine (E), norepinephrine (NE), and thyroxine. Some are water soluble (E and NE) and some are not (thyroxine).

As hormones, **epinephrine** (E) and **norepinephrine** (NE) are both made in the adrenal medulla and both are derived from the amino acid **tyrosine**. As will be discussed in a section ahead, the adrenal medulla as an endocrine gland releases mostly E (**80%**) and NE (**20%**). **Thyroxine** (T_4) is released from the thyroid gland, and made by linking two **tyrosine** amino acids together, with 4 iodine atoms attached to its ring structures (see structure at left). The well know neurotransmitter **serotonin** is also released as a hormone by the pineal gland and by many structures in the gastrointestinal system.



Serotonin is derived from the amino acid **tryptophan**. It turns out that the sleep hormone melatonin is derived from serotonin, so it is also derived from **tryptophan**. **Melatonin** is released by the pineal gland within the brain and regulates sleep wake cycles.

B) Another, perhaps more functional classification of the different chemical structural classes of hormones, is just two basic categories, they are either **lipid soluble** or they are **water soluble**. Below is a summary of the hormones in these two groups.

1. Steroid and Thyroid Hormones: Since these are chemically **hydrophobic** (or **lipophilic**), which means they are not soluble in water but soluble in lipids, they readily pass through the plasma membrane and enter the cytoplasm of the cells in the target tissue. They can also enter the nucleus and bind to chromatin 'receptors' associated with DNA. They have their effects by activating **transcription** of the **DNA**, basically reading a gene, making mRNA and generating various proteins. Steroid hormones often act more slowly than peptide hormones because of the time required to produce new proteins as opposed to activating proteins that are already present. Examples are: Prostaglandins, the sex hormones thyroxin and calcitonin.

2. Peptide and Catecholamine Hormones: Peptide and catecholamine hormones are composed of a short chain of amino acids and the catecholamines are derived from amino acids, especially **tyrosine**. They are **water** soluble (**hydrophilic** or **lipophobic**) and cannot slip into the cell but instead bind to receptors on the outer surface of the cell. In a typical pathway, the resulting complex activates a **G protein**, which then switches on an enzyme that catalyzes the synthesis of cyclic AMP (cAMP) from ATP. Then **cAMP** acts as a **2nd messenger** and activates other enzymes that are inactive inside the cell. In this case, the hormone is the first messenger and cyclic AMP is a second messenger. Examples are: Insulin, glucagon, epinephrine, and the pituitary hormones.

Actions of Lipid-Soluble Hormones

Hormones that are lipid soluble, like the **Steroid** and **Thyroid** hormones, do not need to bind to receptors on the external surface because they pass through the plasma membrane easily, as shown in **Fig. 12.7**. They can bind to internal receptors in the cytoplasm and nucleoplasm.

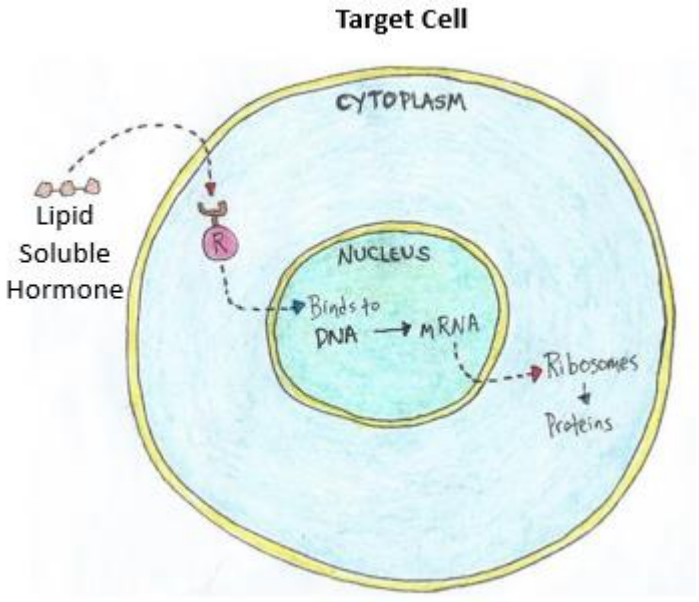


Figure 12.7 Lipid soluble hormones slip past the plasma membrane and move into the cytoplasm, where they bind to internal receptors. These can then move through the nuclear membrane and into the nucleus to influence DNA transcription and the materials (proteins) made as a consequence during translation.

Actions of Water-Soluble Hormones

Hormones that are water soluble, like glycoproteins and peptide catecholamine hormones bind to receptors on the extracellular surface of the plasma membrane. They can then change the cells activity by opening or closing gated ions channels directly ***(ionotropic effect***), or, more commonly in the endocrine system, by activating G proteins on the plasma membrane and generating a 2nd messenger, such as cAMP, that can change the activity of the cell (***metabotropic effect***).

Hormone Interactions

The various hormones released by the many endocrine glands can also interact with one another, adding another shade of complexity to the nature of the endocrine system. There are usually three categories that summarize the most common types of interaction between hormones. They are: **a)** the **Antagonistic** Effect, **b)** the **Synergistic** Effect, and **c)** the **Permissive** Effect. Below are descriptions of these interaction and important examples that exist in the body that will be covered in more detail in this section.

a) *Antagonistic Effect.*

This is when one hormone has an opposing effect of another. One may increase a parameter and the other decreases it.

> **Examples in the Body:**
> **Insulin** and **glucagon** have opposing effects on blood glucose levels. **Parathyroid hormone** and **calcitonin** have opposing effects on blood Ca^{2+} levels.

b) *Synergistic Effect.*

This is when two or more hormones with similar effects produce an amplified response. When the hormones act together they have a greater effect than the sum of them separately.

> **Examples in the Body:**
> **Testosterone** and **follicular stimulating hormone** (FSH) both promote sperm production. **Estrogen** and **progesterone** release at specific times work synergistically in order to coordinate the uterine cycle.

c) *Permissive Effect*.

This is when one hormone enhances the effect of another hormone secreted later. The presence of first hormone enables the subsequent hormone to act to its greatest potential. In this hormone interaction, a hormone cannot exert its full effects without the presence of the other hormone.

> **Examples in the Body:**
> **Cortisol** significantly enhances the effects of **norepinephrine** as a vasoconstrictor. **Thyroxine** also increases beta receptors to amplify the effects of **epinephrine**. **Prolactin** and **oxytocin** are both required for adequate lactation. Prolactin stimulates milk production while oxytocin triggers its release from the breast via the "let-down reflex", thus they appear 'antagonistic' and permissive.

We now have an overview of how the endocrine system works, with the different categories of hormones and the various hormone interaction possibilities. At this point we can begin to explore each of the individual endocrine glands, discovering the hormone or hormones that they release, how they function, their effect on the body and how they are themselves controlled and turned off when their job is done.

The Primary Glands of the Endocrine System

We will start our exploration of the **primary endocrine glands** first, they are the structures whose primary function is to release hormones to regulate body functions. These include the thyroid gland, pineal gland, parathyroid glands, adrenal glands, etc., see **Table 12.1** below for the complete list. These glands function to adjust levels of various substances in the blood and regulate metabolism, growth, the sleep cycle, and other processes. There are **secondary endocrine structures**, these are organs which have other vital functions in the body but also release hormones. These organs include the heart, kidneys, etc., see **Table 12.1** below for the complete list. For the primary endocrine glands, we can start from the top of the body and work our way down! We will then examine the secondary endocrine glands.

Table 12.1. The primary and secondary endocrine glands in the body.

Primary Endocrine Glands	Secondary Endocrine Glands
Pineal gland	Heart
Pituitary glands	Hypothalamus
Thyroid gland	Kidneys
Parathyroid glands	Thymus
Adrenal glands	Ovaries
Pancreas	Testes

The Pineal Gland

Although the pineal gland is located in the **epithalamus**, which is a part of the **diencephalon** of the brain, it is actually an **endocrine gland** because it releases several signal molecules directly into the bloodstream. Therefore, these signal molecules are considered **hormones**.

The pineal gland is the smallest gland in the entire body. The name pineal refers to its resemblance to a tiny pinecone (see **Fig. 12.8 a**). It may be surprising to find out that the pine cone is quite a revered structure throughout history and across many cultures.

Figure 12.8 Shows: **a)** an electron micrograph of a pineal gland, **b)** a 1st century Roman bronze sculpture called the 'Pigna', located in the Vatican 'Court of the Pinecone', and **c)** a pinecone which exhibits the Fibonacci sequence.

This gland is located deep within the center of the brain in humans and is stimulated by signals from the optic nerve of the eyes. It releases several chemical messengers, including **1) Melatonin** and **2) Dimethyltryptamine** (DMT).

1) Melatonin

The main function of the pineal gland is to receive information about the state of the light-dark cycle from the environment and convey this information to produce and secrete the hormone melatonin. There are cells called **pinealocytes** in the pineal gland which produce and secrete the amine hormone **melatonin**, which is derived from **serotonin**. As we know from the introduction, both serotonin and melatonin are **water soluble amines** because they are both derived from the amino acid **tryptophan**.

In a healthy functioning individual, melatonin is released in a **rhythmic cycle** that is dependent the **intensity of light** stimulus. More melatonin is produced at night when there is a natural reduction in the amount of light entering the eyes. Interestingly, in the daytime when light intensity is high the pineal body make serotonin and no melatonin. Conversely, when light intensity decreases, serotonin production stops and melatonin generation and release begins.

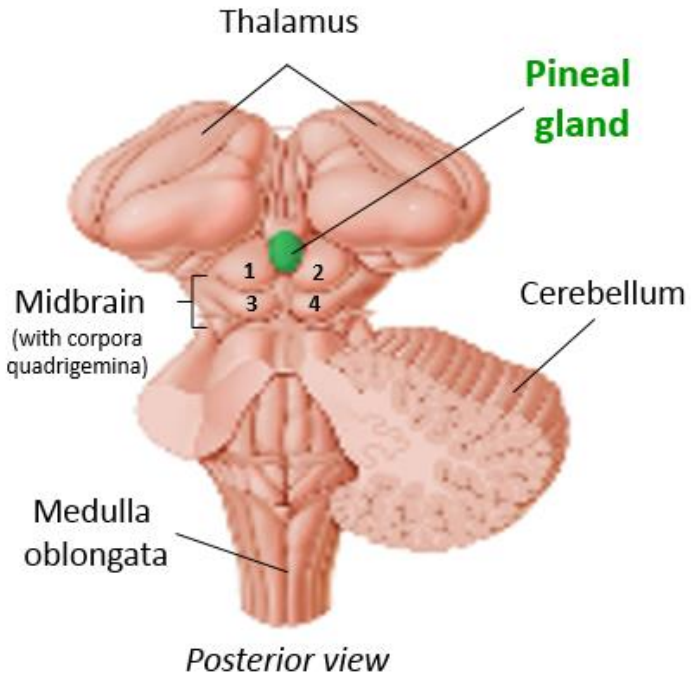


Figure 12.9 Seen here is a posterior view of the diencephalon and brain stem, showing the pineal gland in green sitting directly in between the two hemispheres of the thalamic lobes. The pineal gland is very small and sits on top of the corpora quadrigemina ('quadruple bodies') of the midbrain.

Melatonin Production Pathway

When light enters the eye and captured by the retina, it causes stimulation of photoreceptors which send electrical signal (action potentials) down the retinal-hypothalamic tract to the **suprachiasmatic nucleus** (SCN) of the hypothalamus, which is central in regulating biological and circadian (daily) rhythms. From the suprachiasmatic nucleus, the signal takes a surprisingly long route down to the spinal cord before arriving at the pineal gland (see **Fig. 12.10** below).

If there is sufficient light intensity, e.g., during daytime outside, the SCN reduces the paraventricular nucleus, which has axons that descend to the preganglionic sympathetic neurons of the lateral horn of the spinal cord. These cells adjust the excitability of the superior cervical ganglia neurons, whose axons finally ascend to the pineal gland.

The only inhibitory point in this pathway is from the suprachiasmatic nucleus to the **paraventricular nucleus**. It is the excitation of the SCN by daylight that reduces melatonin production by the pineal gland. Therefore, when the sun goes down (or there is a decrease in any other light source), the inhibition is removed, allowing the excitatory connections in the pathway to increase melatonin secretion. It is the circuits of the brainstem that ultimately control the sleep-wake cycle.

At the cellular level, it is norepinephrine (NE) that regulates the pineal gland activity. When NE binds to its receptors on pinealocytes, it triggers an adenylate cyclase production of cyclic AMP (second messenger), and cAMP assists in the synthesis of melatonin from its precursor **tryptophan**.

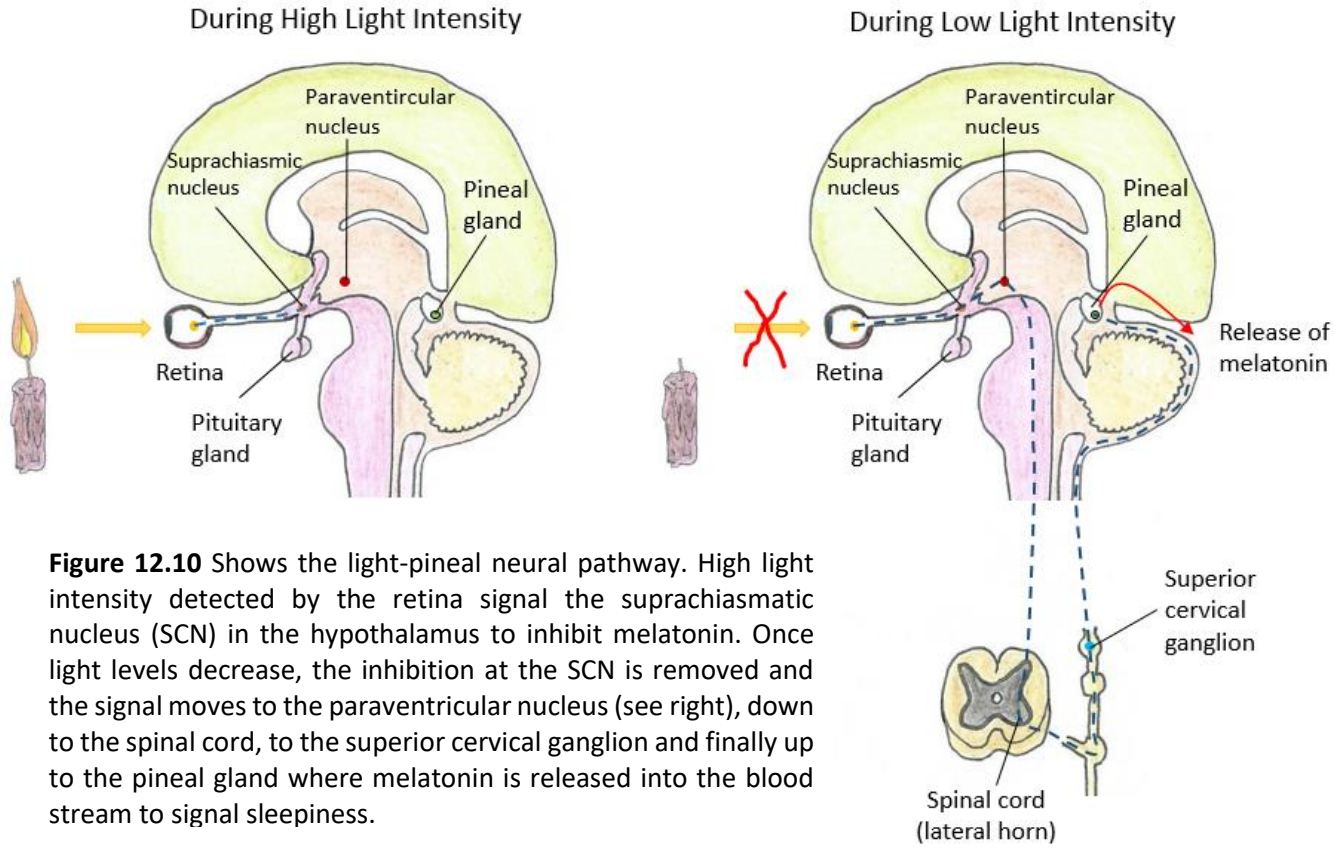


Figure 12.10 Shows the light-pineal neural pathway. High light intensity detected by the retina signal the suprachiasmatic nucleus (SCN) in the hypothalamus to inhibit melatonin. Once light levels decrease, the inhibition at the SCN is removed and the signal moves to the paraventricular nucleus (see right), down to the spinal cord, to the superior cervical ganglion and finally up to the pineal gland where melatonin is released into the blood stream to signal sleepiness.

More Light = Less Melatonin: Less Light = More Melatonin

Now here is the important relationship. When the light intensity is high, the production of melatonin is inhibited. As a result, blood levels of melatonin fall, promoting **wakefulness**. In contrast, as light levels diminish (in the evening), the melatonin production increases, boosting blood levels and causing **drowsiness**. This signals when it is time to go the sleep!

Effects of Melatonin

When melatonin is released into the bloodstream it is carried to tissues in every region of the body, where receptors bind melatonin to regulate the circadian rhythms of the body.

As we saw above, the amount of melanin released depends on the level of light in your surroundings; as light levels decrease, more melatonin is released and this signals the onset of sleepiness; as light levels increase, less melatonin is released and we become more alert and awake.

Melatonin is essential in signaling **relaxation** and also **appetite** and **body temperature**. Interestingly, children have higher melatonin levels than adults, which may prevent the release of gonadotropins from the anterior pituitary, thereby inhibiting the onset of puberty. Finally, an **antioxidant** role of melatonin is the subject of current research.

Jet Lag

When traveling great distances quickly across multiple time zones, it is likely that people will experience some form of jet lag. This is a temporary sleep-cycle disruption due to moving through many time zones. We can see that the changes in day-night patterns would interfere with a person's normal melatonin synthesis and release cycles, disturbing the typical sleep -wake patterns. It can take many days to adapt adjust to the new environment's light and dark cycles and get the body back in sync.

Seasonal Changes in Light and Melatonin

As seasons change in locations away from the equator, there are changes in the length of daylight. Therefore, there are changes in melatonin levels. Animal studies show that melatonin levels have been connected to seasonal mating behavior. For example, when there is a decrease in daylight, the increase in melatonin animal inhibits reproductive functions because the activity of the gonads (ovaries and testes) are depressed. It also signals a winter coat growth and hibernation behaviors. These behaviors are also connected to changes in sex hormone levels. Think of how bears hibernate in the winter, smart move, take a big, long sleep until it gets warmer!

Also, in relation to the daylight cycles of the changing season, some people are adversely affected by the short days and long nights during the winter and experience what's called '**seasonal affective disorder**' (**SAD**). This is a situation in which too much melatonin is produced and can lead to depression, sleepiness, lethargy and weight gain. What could a person do to remedy this? Get more exposure to light!

What Can Block or Alter Melatonin Levels

Several factors can cause low melatonin levels at night. The most common influences are likely **stress**, **exposure to too much light at night** (especially blue light). Night-time melatonin secretion is suppressed by a relatively dim light when pupils are dilated. This has been suggested as the main way through which prolonged use of devices such as laptops and smartphones before bedtime can have a negative impact on melatonin secretion, circadian rhythms and sleep. Also not getting enough natural light during the day affects melatonin production.

Calcification of the Pineal Gland?

The pineal gland also contains a small amount of **calcium** (Ca^{2+}) **hydroxyapatite** (a calcium-phosphorus salt) that is also contained in bone tissue. As it turns out, Sodium Fluoride – which has been added to most municipal water supplies - is attracted to Ca^{2+} hydroxyapatite crystals like a magnet and this can cause the pineal gland to become 'calcified' with sodium fluoride and other salts. If melatonin levels are suppressed by this calcification, this can shorten the time to the onset of puberty.

Recent studies show a dramatic *decrease* in the age for the onset of menstruation (menstrual period) for girls in developed countries, including the United States. Even 20 years ago the onset of puberty for girls

was from about **12 to 14** years of age. More recently, in some areas it is as early as **7 to 9** years of age. Although this situation is likely to have many aspects and possible co-factors to it, the development of the trend is harmful. Research has compellingly shown that the earlier the onset of puberty is, the shorter the lifespan of the individual.

The Fibonacci sequence and the Seat of the Soul

Historically, the pineal gland was described as the "Seat of the Soul" by Renee Descartes. Some currently suggest the pineal gland is the biological relative of the energetic third eye chakra and it is often referred to as the "spiritual third eye" because it is regarded as the gateway to spiritual life as per ancient concepts about the soul. An interesting aspect of this is the presence of photoreceptors on the pineal gland, even though in most animals (including humans) the pineal gland is not directly exposed to light.

The **Fibonacci** sequence a mathematical formula that can be seen in patterns found in nature and the natural world. Each number in the sequence is the sum of the previous two numbers, as follows: 0, 1, 1, 2, 3, 5, 8, 13, 21, 34, 55, 89, 144, etc. to infinity!

The ratio between numbers within the Fibonacci sequence is always = **1.6**, the symbol for this number is ϕ (phi), which is called the **Golden Ratio**. The golden ratio is sometimes called the "divine proportion," because its frequency is replete in the natural world (see **Fig. 12.11** below). This geometry is also found in the **Golden Spiral**, which is a logarithmic spiral whose growth factor is 1.6 or ϕ. The shape is infinitely repeated when magnified. This pattern can be seen when looking at nature under the microscope and through a telescope.

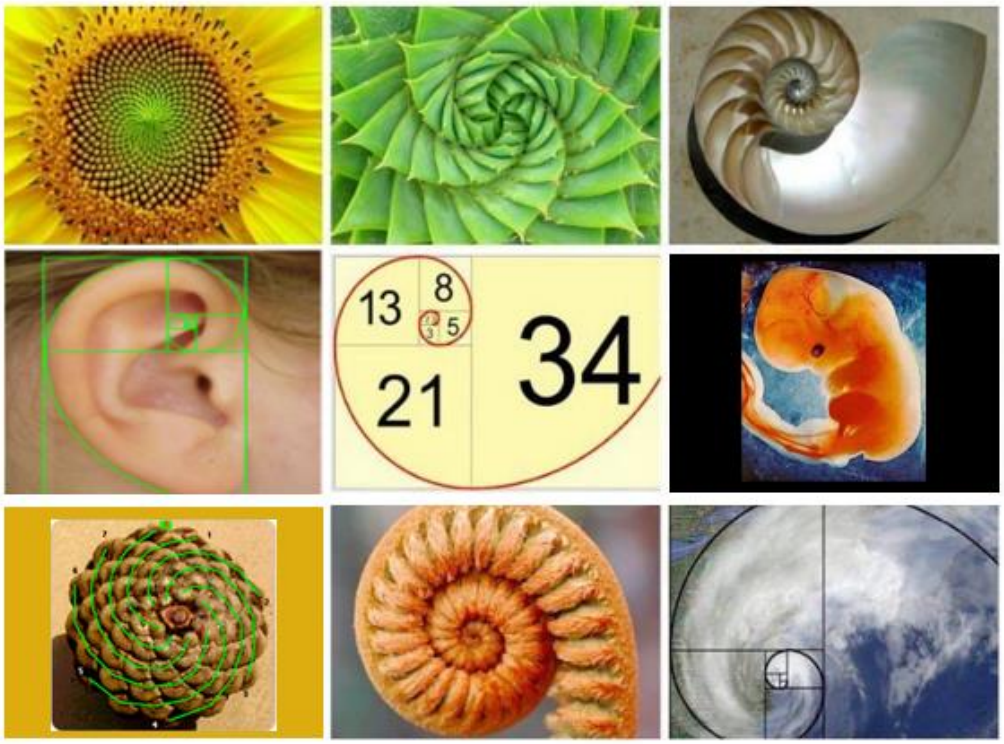


Figure 12.11 These images show the myriad of examples in the natural world which contain the Fibonacci sequence (or number). Note the center panel showing the 'golden spiral' that follows the Fibonacci sequence with the repeated golden spiral (ϕ). The seeds of a sunflower, the number of petals on a flower, the spiral of a shell, the arrangement of the human ear, the position of a fetus, the twist of a pinecone in opposing spirals, plant growth and the movement of weather patterns. All of these natural structures contain the Fibonacci sequence.

2) Dimethyltryptamine (DMT)

Dimethyltryptamine or **DMT** is one of the most powerful hallucinogens of the tryptamine family. Not only do humans make DMT themselves in their pineal glands (we have our own endogenous supply), but it is also ubiquitous in many plants. DMT is believed to be released in significant amounts at three specific times in life: **a)** during birth, **b)** during lucid dreaming and **c)** during near-death experiences (in situations of extreme duress). It is thought to play a role in facilitating the visual aspects of dreaming during sleep, spiritual visions and experiences in deep meditation. There are books written about this molecule, declaring DMT the "Spirit Molecule". Structurally it is very similar to the neurotransmitter **serotonin** (5-HT), which is of course also very similar to **melatonin**, all of which are released by the pineal gland.

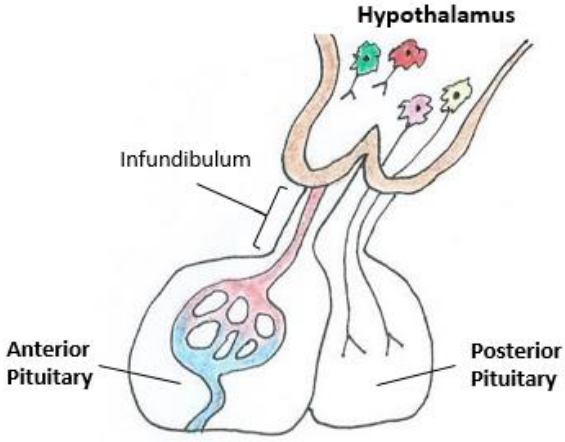
In traditional South American practices, ayahuasca vine is prepared as a drink containing high levels of DMT, along with other plants that have monoamine oxidase (MAO) inhibitors. Thus, when drinking it, the active DMT will not be enzymatically degraded by MAO inhibitors in the stomach. This is considered a *medicine* and not a 'recreational drug', as it is used for spiritual, emotional, physical and mental healing.

The Pituitary Gland

The **pituitary gland** is another endocrine structure that is located in the brain and is connected to and closely associated with the **hypothalamus**. The pituitary gland is actually two separate glands that operate very differently. They are the anterior pituitary gland (in the front), and the posterior pituitary gland (in the back).

As we will see below, technically we can consider the hypothalamus an endocrine gland. Many decades ago, the hypothalamus was termed the master endocrine gland as its role in so many other endocrine glands in the body was being recognized. In this text we will show how the hypothalamus acts through both the anterior and posterior pituitary glands using different mechanisms.

The **pituitary gland**, shown in **Figures 12.12-13** below, is also referred to as the ***hypophysis*** as it is located directly *under* the hypothalamus. The pituitary gland is really two separate glands, both are under the control of the hypothalamus. The two distinct regions in the gland are:



The **Anterior Pituitary** (also called the ***Adenohypophysis***).

The **Posterior Pituitary** (also called the ***Neurohypophysis***).

The anterior pituitary (see **Fig. 12.12**) is called the adenohypophysis because the term **adeno** means 'gland', indicating that this portion makes and releases all of its own hormones. The activity of the adenohypophysis is controlled by releasing and inhibitory hormones from the hypothalamus.

Figure 12.12 The drawing above shows how the hypothalamus connects to the pituitary by the infundibulum.

The posterior pituitary (see **Fig. 12.11**) is called the neurohypophysis because the term **neuro** means nervous system, and this portion is really nervous tissue, not glandular tissue. It is actually a continuation of brain tissue. Also, the two hormones it releases are *made* by the hypothalamus and *stored* in the

posterior pituitary until a signal from the hypothalamus stimulates their release. The neurohypophysis is completely controlled by nervous stimulation by the hypothalamus.

In order to fully understand the nature of the communication between the hypothalamus and the anterior and posterior pituitary glands, we need to adequately describe the **hypothalamic–hypophyseal tract** and the **hypothalamic–hypophyseal portal system**.

Hypothalamic-Hypophyseal Tract

The posterior pituitary is an extension of nervous tissue from the **paraventricular** and **supraoptic** nuclei of the hypothalamus. There are two groups of cell bodies in the hypothalamus but their axons descend into the posterior pituitary via the **hypothalamic–hypophyseal tract** through the infundibulum (see **Fig. 12.13** at right). They terminate in the posterior pituitary where the hormones (made by neurons) are released.

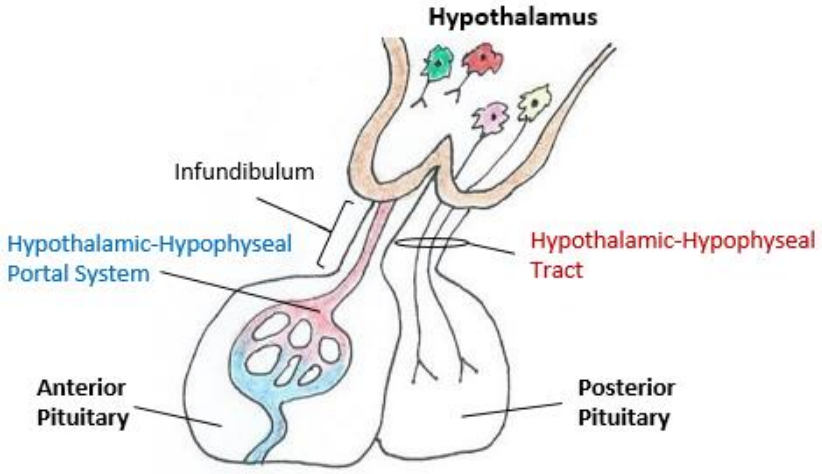


Figure 12.13 Within the infundibulum, is: **1)** the hypothalamic-hypophyseal tract, and **2)** the hypothalamic-hypophyseal portal

Hypothalamic-Hypophyseal Portal System

The communication between the anterior pituitary and the hypothalamus also occurs within the infundibulum, but here it is a system of capillaries that connects the two. This arrangement is called the **Hypothalamic-Hypophyseal portal system,** in the cardiovascular system a **portal system** is a vascular arrangement linking 2 different capillary beds in series from one organ to another by connecting vessels. In this location it is called the hypothalamic-hypophyseal portal system connecting the hypothalamus to the anterior pituitary.

This special system allows the **neuro-hormones** that are secreted by the neuroendocrine cells of the hypothalamus to be transported directly to the cells of the anterior pituitary gland. These hormones from the hypothalamus are largely, but not entirely, excluded from the general circulation.

OK, we needed to get that foundation laid first regarding how each of the parts of the pituitary gland (the anterior and posterior) communicate with the hypothalamus, that being by way of the hypothalamic-hypophyseal **portal system** (for anterior) and hypothalamic-hypophyseal **tract** (for posterior).

Now that we know how the hypothalamus communicates with the pituitary gland, let's start looking at the two very distinct structures of this gland, starting with the posterior pituitary gland.

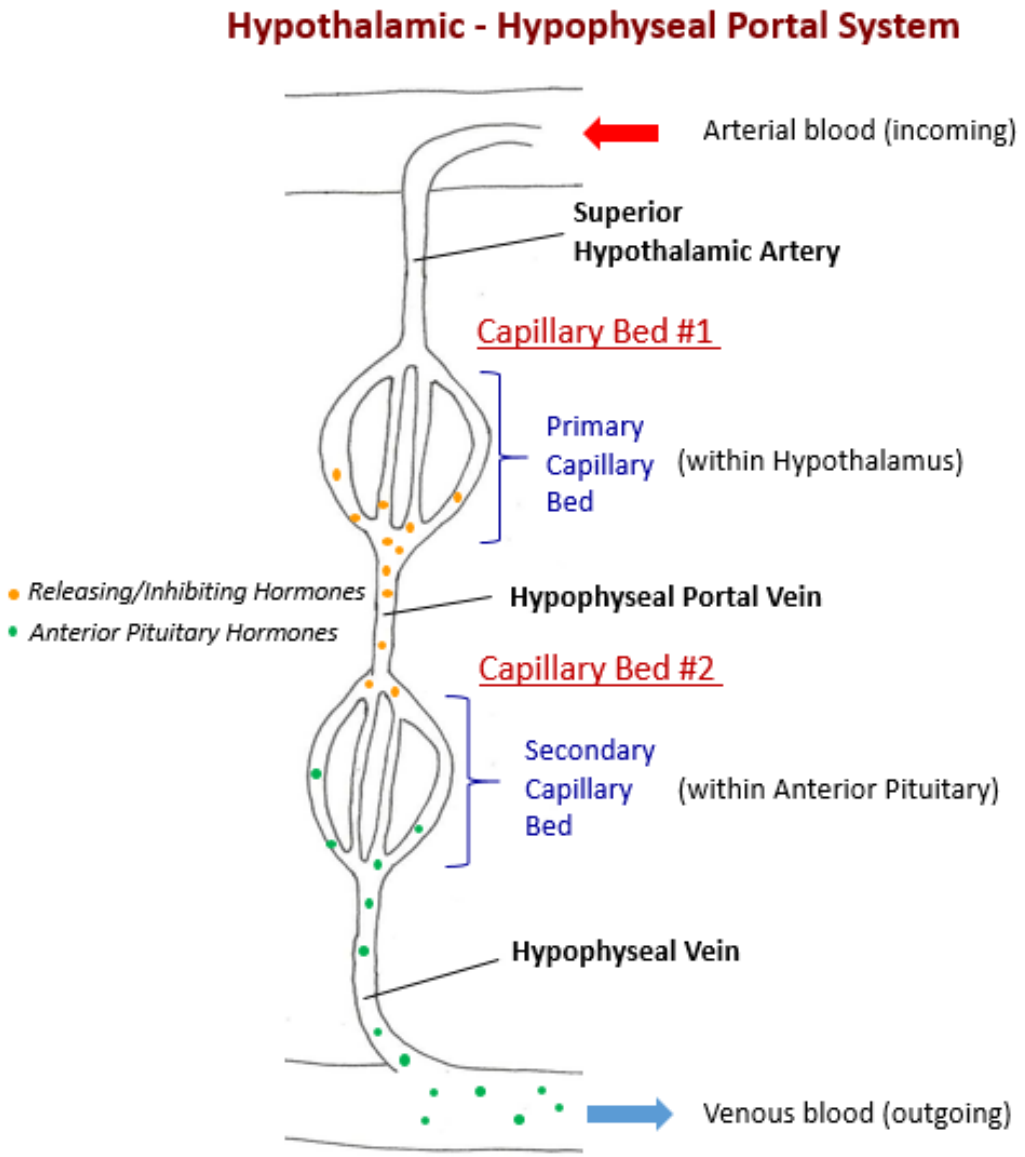


Figure 12.14 This diagram shows the hypothalamic-hypophyseal portal system between the hypothalamus and the anterior pituitary gland. The system originates from the branches of the superior hypothalamic artery, branching from the carotid arteries into the hypothalamus. The Hypothalamic releasing and inhibiting hormones travel through a primary capillary bed to the hypophyseal portal vein into the anterior pituitary. Hormones produced by the anterior pituitary (in response to releasing hormones) enter a secondary capillary bed and from there enter into the circulation.

The Hypothalamic hormones (which have either inhibiting or stimulating effects on the adenohypophysis) are secreted by neurons there and they travel to the anterior pituitary via this hypothalamic-hypophyseal portal system of blood vessels. The zoomed in view of the specific arrangement is seen in **Fig. 12.15** below.

Posterior Pituitary (Neurohypophysis)

It's good to start with the posterior pituitary or **neurohypophysis** because it simpler and only has 2 hormones. As displayed in **Fig. 12.15** below, the posterior pituitary contains axons of neurons that extend from the hypothalamus into the posterior pituitary via the infundibulum (the stock connecting the hypothalamus to the pituitary gland).

The two hormones of the neurohypophysis are: **1)** Oxytocin and **2)** Antidiuretic Hormone (ADH).

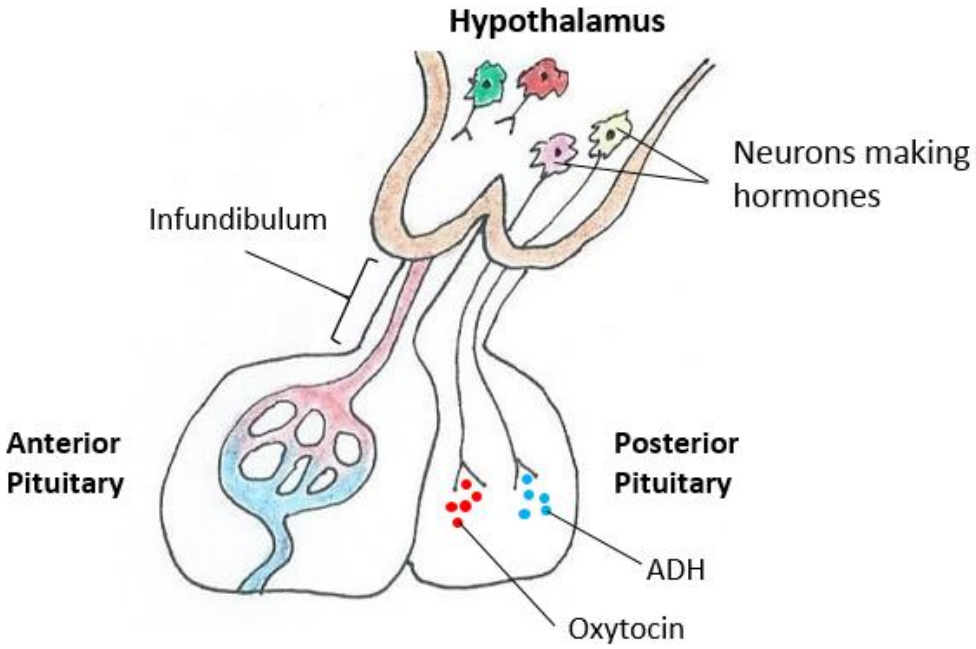


Figure 12.15 This drawing shows relationship between the hypothalamus and the posterior pituitary gland. It is actually two populations of neurons in the hypothalamus that make the two hormones oxytocin and antidiuretic hormone (ADH) that are stored in and released by the posterior pituitary gland.

1) Oxytocin

The peptide hormone oxytocin is important for its action to stimulate the smooth muscle of the uterine walls within the layer called the myometrium during **childbirth**. This causes the significant contractions of the uterus that occur during childbirth or 'labor'. The positive feedback loop is below. This hormone also stimulates the **release of milk** from the mammary glands by causing surrounding cells to contract. After birth, stimulation of the breast by the infant feeding stimulates the posterior pituitary to produce additional oxytocin.

Positive Feedback Loop in Homeostasis:

The release of oxytocin during childbirth is a great example of a positive feedback loop in human physiology. **Fig. 12.16** exemplifies this as follows: As birthing time approaches, the baby's head pushes against the cervix of the uterus and increases pressure on the cervix, which is where the baby is going to travel through. Stretch sensitive receptors there detect this and send afferent signals to the **posterior pituitary**. This triggers release of **oxytocin** from the posterior pituitary into the blood stream, which binds to receptors on the smooth muscle of myometrium and causes the body of uterus to contract, pushing the baby's head more firmly against the cervix, increasing the pressure, which triggers more oxytocin release, so the cycle continues, and becomes amplified until it is broken! (= birth occurs).

The Role of Oxytocin in Childbirth and the Positive Feedback Loop

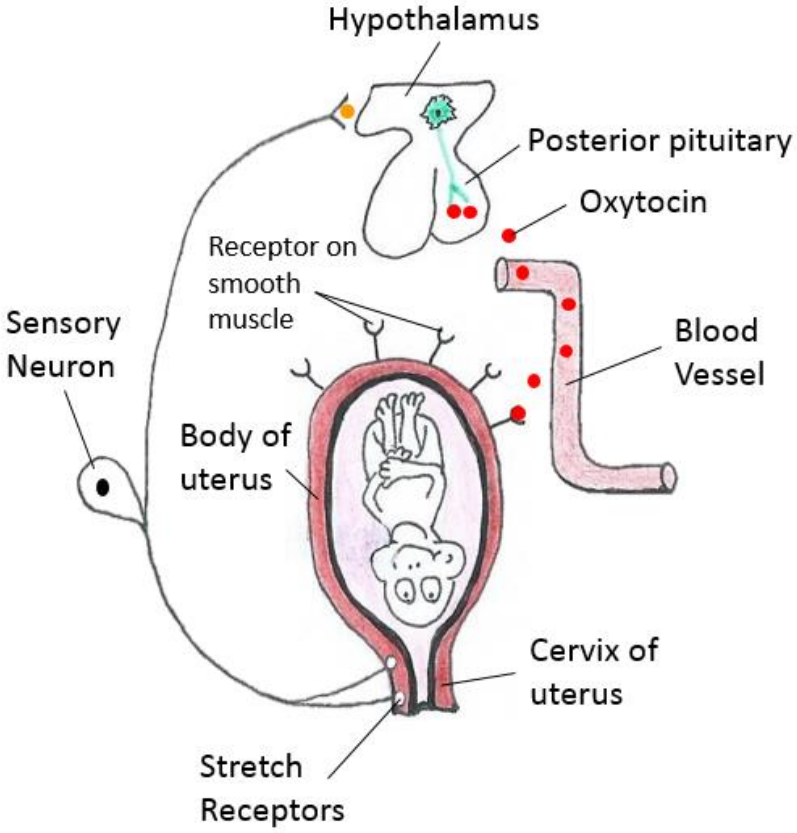


Figure 12.16 This diagram shows the role of oxytocin during childbirth using a positive feedback loop to homeostatically regulate and oversee the childbirth process. The loop commences once the baby's head moves and applies pressure on the cervix. Moving around the diagram in a type of clock-wise manner the result of the loop is contraction of the body of the uterus which increase pressure on the cervix, repeating the loop until it is broken by the birth of the baby.

Oxytocin: The Bonding Hormone

More recently the role of oxytocin in human bonding has been examined and it has been revealed to be significantly involved in **human bonding**, and feelings of 'love' and is often referred to as the 'bonding' hormone. It has long been known that oxytocin plays a critical role in the bonding between a mother and her infant, specifically with regard to physical **touch** and **olfaction**. Human touch and expressions of love are essential to health. A lack of stimulus and touch very early on causes excess **cortisol** release (also related to elevated stress) which can create a toxic brain environment and damage certain neural structures.

The Importance of Human Physical Touch

Research in neuroscience shows that the easiest and quickest way to induce **depression** and **alienation** in an infant or child is not to touch it, not to hold it, not to carry it on your body. It should not be surprising that this also applies to adults, though normal development is significantly hindered in children deprived of warm human physical contact. Imagine how many people have now become fearful of touching their children because some mysterious virus might be present. It can be argued that the real damage has not arisen from an unseen particle but from the unhealthy choices made trying to avoid an invisible enemy.

Previous to all the COVID hysteria, it had been proposed and essentially universally understood that a lack of physical touch damages not only individuals, but our entire society. Ultimately, human sensory deprivation can result in ***significant*** behavioral abnormalities such as depression, violent behavior, substance abuse, and an impaired immunological functioning in mother deprived infants. All of these conditions have risen since the edict of 'social distancing' (which has no foundation in science) were implemented. Hopefully people have come to have enough common sense not to follow ridiculously unscientific advice when it clearly only causes harm and has no benefit at all.

Oxytocin is not just for Babies!

Not only is oxytocin critical in mother-infant bonding, oxytocin is also associated with the act of closeness and touching between adult humans, where this hormone helps to create an **emotional bond** between people. For example, a study shows that even the simple act of sharing a meal with another person increases your levels of oxytocin. Additionally, for adults during sexual intercourse both females and males release high levels of oxytocin. In this capacity, oxytocin is released as a **pheromone**, a signal molecule that is secreted outside of the body to communicate with others.

With regard to pheromones, the **vomeronasal organ** (**VNO**) is located the nasal cavity near the vomer bone which forms the lower portion of the bony nasal septum. Related to olfaction (sense of smell), the VNO is composed of receptors for sensory nerve cell bodies that detect specific non-volatile (liquid) organic compounds conveyed from the environment. As indicated above, in humans and other animals, these compounds called pheromones can have a powerful impact on the behavior and physiology of others. Stimulation of the VNO by pheromones typically triggers an appropriate behavioral response to the specific signal molecule. Many of the phenomes released are categorized as sex pheromones since they are related to attraction.

There is also a literal connection of touch and bonding to another organ, the heart. A researcher in 1992 described a dual role of the heart cells: Not only do heart cells contract and expand rhythmically to pump blood, but they also communicate with each other. If a single heart cell (myocardiocyte) is isolated from others around it, it loses its rhythmicity and begins to fibrillate and die. If, however, one isolated heart cell is placed in close proximity to another, they synchronize and beat in unison and do not die. Perhaps this is why most mothers instinctively place their newborn babies on their left breast, keeping their hearts in close proximity to each other so they can synchronize and connect better. Link to Baby video*

2) Antidiuretic Hormone (ADH)

Antidiuretic Hormone (ADH) is also known as **Vasopressin**, they are the same molecule but discovered by different researches in different areas of the body. This hormone is released in response to the body's need to conserve water. When a person is dehydrated this is detected by **osmoreceptors** located in the hypothalamus. They monitor the osmolarity of blood and are stimulated into action if the osmolarity rises (becomes more concentrated) as this is a sign of dehydration.

Because of the hypothalamic-hypophyseal portal system (described earlier), the normally restrictive **blood brain barrier** of the hypothalamus is incomplete. This allows for the hypothalamus to monitor systemic blood and detect its osmolarity. The tradeoff is that region is therefore susceptible to substances gaining entry into the cerebrospinal fluid (CSF) because of the incomplete blood brain barrier here.

To be specific, if the osmolarity of the blood is over 310 mOsM it is considered hypertonic (too concentrated). These receptors detecting this change in blood osmolarity send signals to the **lateral hypothalamic area** in the hypothalamus which triggers the release of **ADH** from the posterior pituitary.

The ADH travels in the blood stream to its target tissue, which is the distal convoluted tubules and the collecting ducts associated with the nephrons of the kidney. The epithelial cells lining these regions are stimulated to produce and insert **water pores** (aquaporins) in these regions. This results in more water being reabsorbed (retained) by the body, hence less water loss occurring in the urine, making the urine more concentrated as water is conserved by the body.

The alternate name for ADH is **Vasopressin** and its name implies another function. The vaso part = vessel, and the pressin = pressure, and as it turns out, this hormone also acts as a **vasoconstrictor** for blood vessels and can elevate blood pressure. If a person were experiencing cardiovascular shock, for example, the actions of conserving water, together with increasing blood pressure is a very effective way for the body to re-establish adequate blood pressure and maintain homeostasis. Thus, the important role of ADH in safeguarding the body is seen here.

Alcohol and ADH

Drinking alcohol is known to be a **diuretic**, that is, something that causes an increase in urine output. When consumed, alcohol causes diuresis by inhibiting ADH. This reduces the number of water pores in the collecting duct, and results in greater water loss in the urine. The unpleasant feelings of a 'hangover' can in part be attributed to the dehydration caused by the inhibition of ADH release by the alcohol.

Diabetes Insipidus

The disease **diabetes insipidus** is not very common but is related to ADH. It is characterized by a decrease in ADH release which results in an excessive amount of urination (**polyuria**) leading to dehydration. It is often also associated with increases in thirst (**polydipsia**) and increases in appetite (**polyphagia**). In cases of diabetes insipidus the urine is **very dilute** and in the past health care workers had to "test" a patience's urine by tasting it, and they'd routinely report it to be 'tasteless' or 'insipid', hence its name.

The Hypothalamus and the Posterior Pituitary Gland

Just to reiterate, the hypothalamus significantly regulates the function of both the anterior and posterior pituitary glands. It sits right above both lobes of the pituitary gland (see **Fig. 12.17**). To be succinct because it was covered immediately above, the **neurosecretory cells** of the hypothalamus actually make the hormones of the posterior pituitary gland **antidiuretic hormone** (ADH) also known as vasopressin, and **oxytocin**. These two hormones are **stored** in and **released by** the posterior pituitary.

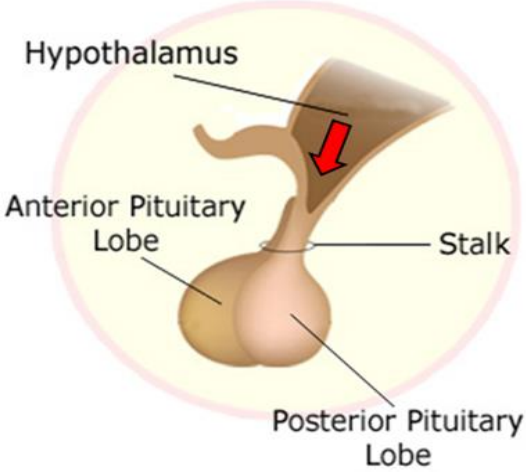


Figure 12.17 A diagram showing the relationship of the hypothalamus to the two lobes of the pituitary gland, connected by the infundibulum or stalk.

The Hypothalamus and the Anterior Pituitary Gland

Regarding the hypothalamic control of the anterior pituitary gland, as described in detail previously above, the **hypothalamic-hypophyseal portal system** allows for the hypothalamus to send releasing and inhibiting hormones to the anterior pituitary gland. Hormones made by the anterior pituitary (in response to releasing hormones) are released systemically to have their effects. Sometimes the term **neurohormone** is used to describe the substances that the hypothalamus secretes that initiates or stops the secretion of anterior pituitary hormones.

The Hormones of the Hypothalamus

We can refer to these hypothalamic substances as hormones since they do take a journey in the circulation, albeit and very short one downstream to the anterior pituitary.

Inhibiting hormones of the Hypothalamus:

- **Growth hormone-inhibiting hormone** (GHIH), also known as **somatostatin** (soma = body, stasis = stagnation, staying the same), as both names imply, it inhibits the release of growth hormone, and also acts as a strong manager of growth throughout the body.

- **Prolactin-inhibiting hormone** (PIH) inhibits the release of the hormone prolactin and thereby inhibits milk production.

Releasing hormones of the Hypothalamus:

- **Corticotropin-releasing hormone** (CRH). This hormone stimulates the anterior pituitary gland to release **adrenocorticotropic** hormone (ACTH) which then circulates and stimulates the adrenal glands to release corticosteroids, like cortisol, which help regulate metabolism and immune response.

- **Growth hormone-releasing hormone** (GHRH), which stimulates the anterior pituitary to release **growth hormone** (GH) which effects essentially all tissues in the body, enhancing growth and repair.

- **Prolactin-releasing hormone** (PRH), which prompts the anterior pituitary to release prolactin (PRL), the hormone which stimulates mammary glands to produce breast milk.

- **Thyrotropin releasing hormone** (TRH), stimulates the anterior pituitary to release **thyroid stimulating hormone** (TSH), which then promotes the growth of the thyroid gland and release of thyroid hormones, which regulate metabolism, energy, growth and development throughout the body.

- Gonadotropin-releasing hormone (GnRH), which triggers the anterior pituitary to release **follicular stimulating hormone** (FSH) and **luteinizing hormone** (LH), both of which influence the gonads (ovaries and testes) and the development of the gametes (egg and sperm cells).

Anterior Pituitary (Adenohypophysis)

The name **adenohypophysis** denotes that it is glandular tissue (adeno = gland). The hypothalamus produces hormones (hypothalamic-releasing and inhibiting hormones) that travel in blood vessels to the anterior pituitary, stimulating (or inhibiting) it to produce other hormones. The anterior pituitary produces **7 different hormones**. Each one is produced in response to a specific hypothalamic-releasing hormone. There are also hypothalamic-inhibiting hormones which prevent the production and release of hormones from the anterior pituitary (see **Fig. 12.18** below).

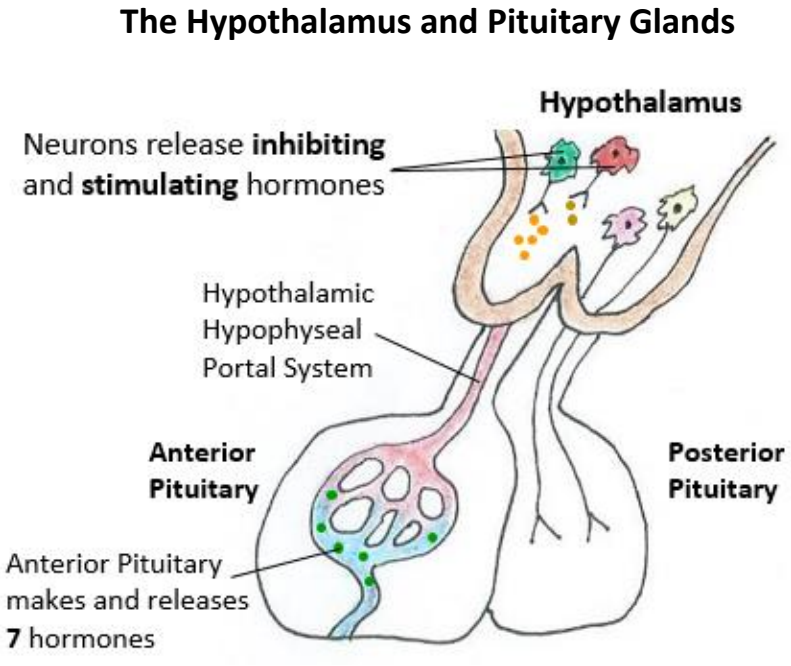


Figure 12.18 This drawing shows relationship between the hypothalamus and the anterior pituitary gland. There are two populations of neurons in the hypothalamus that make inhibiting and releasing hormones that travel down the hypothalamic–hypophyseal portal system to the anterior pituitary which triggers the inhibition or release of six hormones.

The anterior pituitary produces **seven (7) hormones**. They are: Human growth hormone (GH), thyroid-stimulating hormone (TSH), adrenocorticotropic hormone (ACTH), follicle-stimulating hormone (FSH), luteinizing hormone (LH), prolactin (PRL) and finally beta endorphin. The first four hormones listed (TSH, ACTH, FSH, and LH) are referred to as **tropic** hormones (trope means' turning' or 'to turn') because they turn on or off the function of other endocrine glands.

The Seven (7) hormones released by the **Anterior Pituitary Gland** are:

1. Growth Hormone (GH), often denoted as human growth hormone (hGH)
2. Thyroid Stimulating Hormone (TSH)
3. Adrenocorticotropic Hormone (ACTH)
4. Follicle-stimulating Hormone (FSH
5. Luteinizing Hormone (LH)
6. Prolactin (PRL)
7. Beta-endorphin

Brief Summary of the 6 hormones from the Anterior Pituitary:

1. **GH (hGH)** – is the primary hormone that regulates overall body development, growth, and repair. It is also important in general metabolism, mostly promoting anabolic activities. Severe GH deficiency during growth phases leads to dwarfism. Over-secretion of GH in children leads to gigantism. Severe over-secretion of GH in adults' leads to acromegaly, a genetic disorder in which GH is over-produced throughout a person's lifetime.

2. **TSH** – stimulates secretion of **thyroxine** from the thyroid gland and stimulates the growth of the thyroid gland. It is an important regulator of metabolic activity in the body.

3. **ACTH** – stimulates **cortisol** secretion from the adrenal cortex (often called the 'stress hormone', but in appropriate levels, cortisol is your friend). Also promotes growth of adrenal cortex.

4. **FSH** – **a)** in females: stimulates growth and maturation of the **ovarian follicles**, and promotes estrogen secretion. **b)** in males: it is required for **sperm production** (together with ICSH).

5. **LH** – **a)** in females: responsible for **ovulation** and for luteinization. Regulates estrogen and progesterone. **b)** in males: stimulates interstitial cells (in testes) to secrete **testosterone**, and therefore in males it's typically called interstitial cell stimulating hormone (ICSH).

6. **PRL** – **a)** in females: high quantities after childbirth, it enhances breast development and stimulates mammary gland development for the **production of milk**. Oxytocin enhances the effects of PRL on **expression of milk**. **b)** in males: it enhances LH-receptors in interstitial (Leydig) cells increasing **testosterone**, thus increasing **spermatogenesis**. Also stimulates oligodendrocyte precursor cells.

7. **β-Endorphins** – an opioid peptide acting as a hormone when released by the anterior pituitary gland. It **blocks the sensation of pain**, and is released in response to intense pain, strenuous exercise or types of stress (see this information in chapter 8 on neurotransmitters). The anterior pituitary releases β-endorphin and enkephalins simultaneously with **adrenocorticotropic hormone** (ACTH) during exercise, followed by a delayed release of **cortisol.**

Tropic and Trophic Hormones

The terms **tropic** and **trophic** actually have different meanings. As discussed above briefly, **tropic** hormones can turn on or off other **endocrine** glands, thereby influencing their activities. Whereas 'non-tropic' hormones directly stimulate other non-endocrine tissue.

Trophic hormones specifically mean **growth** stimulatory effects on their target tissues. Does this seem OK? For example, Thyroid Stimulating Hormone (TSH) and Adrenocorticotropic Hormone (ACTH) are tropic, but cortisol or ADH are non-tropic hormones.

It may be most effective to focus on this list below to see how hormones released by the anterior pituitary have their effects:

- **Somatotrophs** = 'body growth': Are cells in the anterior pituitary that release **growth hormone** (**somatotropin**). They represent about 30-40% of the cells in the anterior pituitary.

- **Gonadotrophs** = 'gonad growth': Cells in the anterior pituitary that secrete **gonadotropins** such as the follicle-stimulating hormone (**FSH**) and luteinizing hormone (**LH**).
- **Corticotrophs** = 'adrenal cortex growth': Anterior pituitary cells make corticotropin-releasing hormone (**CRH**) to stimulate synthesis and secretion of adrenocorticotropic hormone (**ACTH**).

Conditions Required for Normal Growth and Repair

For normal body growth and repair to occur in the body across all ages and stages of development, these are the main conditions needed:

- **Adequate** and **appropriate** levels of **growth hormone** and other regulatory hormones.

- An **adequate diet**, ensuring quality sources of carbohydrates, lipids and proteins, as well as vitamins and minerals.

- The **absence of stress**, especially chronic (long term) stress.

- A healthy regulation of **gene expression** and modification.

The people shown in the photo to the right (**Fig. 2.19**) are examples of what can occur if the growth hormone (GH) levels are not adequate and appropriate. Severe GH deficiency leads to **dwarfism**, the man in the photo is 2 feet, 5.4 inches in height. Over secretion of GH in children leads to **gigantism** the man in the photo is 8 feet, 1 inch in height. Over secretion of GH in adults leads to acromegaly, which can result in thickening and enlargement of bony structures of the face, hands, and feet. Could there have been very tall, giant-like humans in the past? There have also been plenty of claims of finding amazing skeletal remains, **Fig. 12.17** below.

Figure 12.19 Evidence of across the world of giant skeletons is not uncommon (right). The variation in the stature of the human form is also shown comparing a midget to an exceptionally tall man (left)

The Agouti Mice Experiment

Agouti mice are distinguished by their unique characteristics of a **yellow fur** (rather than white or brown), **obesity**, they exhibit **hyperinsulinemia** (too much insulin in the blood), insulin resistance, **hyperglycemia**, and **hyperleptinemia** (excessive levels of the hormone **leptin** in the blood.

In the agouti mouse, the **agouti protein** is overproduced, and the overproduced protein greatly inhibits the effects of a hormone **melanocyte-stimulating hormone** (MSH). The yellow mouse obesity syndrome is due to dominant mutations at the Agouti locus, which is characterized by obesity and other issues.

This syndrome is caused by **ectopic** expression of Agouti in multiple tissues. The yellow agouti mouse has been a great animal model with which to study **epigenetics**. Epigenetics is the study of how behaviors and environment (such as nutrition and thoughts) can changes the way your genes work. Epigenetic factors change how your body reads and expresses a DNA sequence, or a gene. In the year 2000, a study (**Fig. 12.20**) showed that dietary factors can prevent the agouti gene from being turned on!

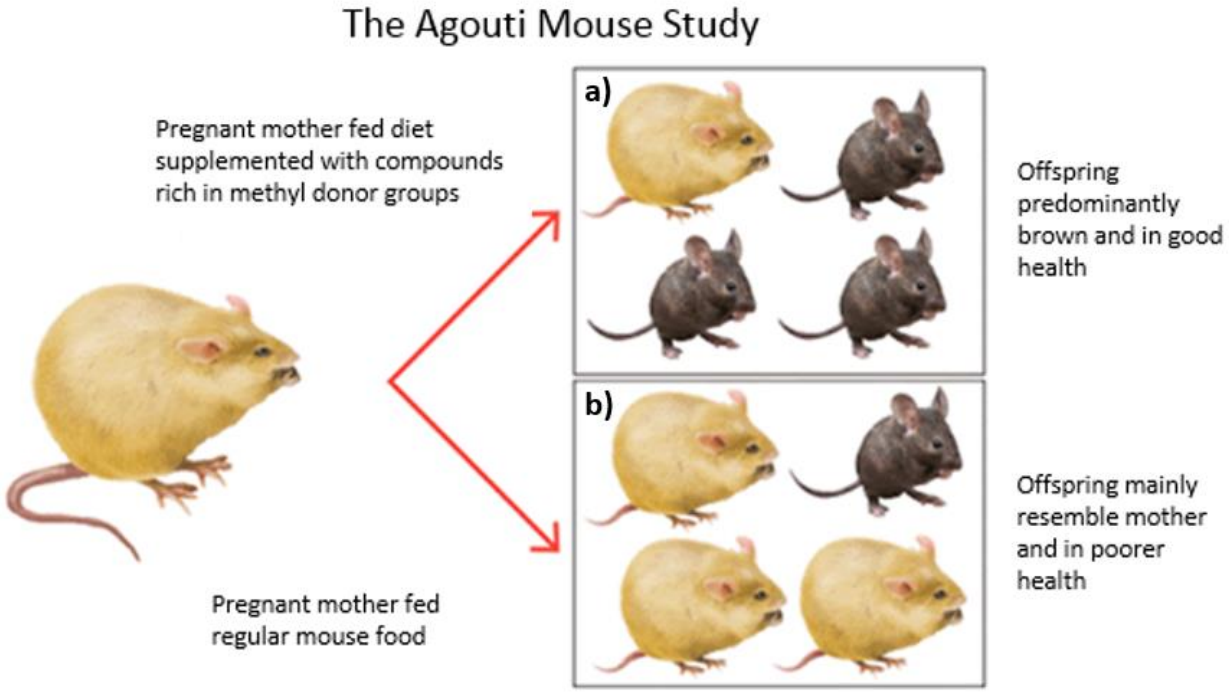


Figure 12.20 This shows a summary of the Agouti mice study. The diet of the Agouti mother was wither supplemented with choline, folic acid, betaine and vitamin B_{12}, or she was fed regular mouse food. The offspring from the mother feed the nutrient rich diet are shown in the top panel **a)** showing the majority have the healthy phenotypic expressions (fur color and size etc.), whereas the offspring from the mother feed regular mouse food in the top lower panel **b)** show the majority have the Agouti phenotypic expressions (yellow, obese, etc.),

The results from the study show that nutrition during development in the womb influences the mice. It also shows that not only is our health determined by what we eat, but also what our parents ate. Particularly important is the mother's diet, as it helps to shape the **epigenome** of her offspring.

The nutrient rich diets contained methyl-groups (e.g., vitamins B_9 and B_{12}) that **switched off** the agouti gene in the offspring. This is because a methyl-rich diet provides “methyl donors” to DNA which yielded protective measures to gene expression. This resulted in brown and thin mice with, not yellow and obese (see **Fig. 12.20**). The obese yellow and skinny brown mice are **genetically identical**, it is the **phenotype** or the physical expression of the gene that has been altered. The obese yellow mice are different because

they have an epigenetic "mutation" that is ***expressed*** - due to lack of methyl donors (good nutrition) in their diet. Note: Exposure of the cute mice to bisphenol A (BPA) during pregnancy increased the incidence of yellow offspring.

As discussed in digestion, **leptin** is a hormone released from the adipocytes (fat cells) in adipose tissues. It signals the satiety center in the hypothalamus and helps regulate and alter long-term food intake and energy expenditure, not just from one meal to the next. Leptin is a mediator of long-term regulation of energy balance, suppressing food intake and thereby inducing weight loss. **Ghrelin** on the other hand is a fast-acting hormone that triggers the feelings of hunger, seemingly playing a role in meal initiation.

The Thyroid Gland

The thyroid is a butterfly-shaped gland in the neck, sitting just under the thyroid cartilage of the larynx and just over the top portion of the trachea, as can be seen below. Normally it should weigh less than an ounce (about 30 g). During development in utero, the thyroid gland originates in the back of the tongue and migrates to the front of the neck. In rare instances it sometimes fails to migrate properly and stays very high in the neck much closer to the tongue; other times it may migrate too far and end up in the chest.

The thyroid hormones include: **1) Thyroxine** and **2) Calcitonin**. They regulate metabolic rate, growth, and development throughout the body. This gland is composed of follicles which can be seen in histological slides, these structures produce the hormone precursor thyroglobulin.

The Thyroid Gland

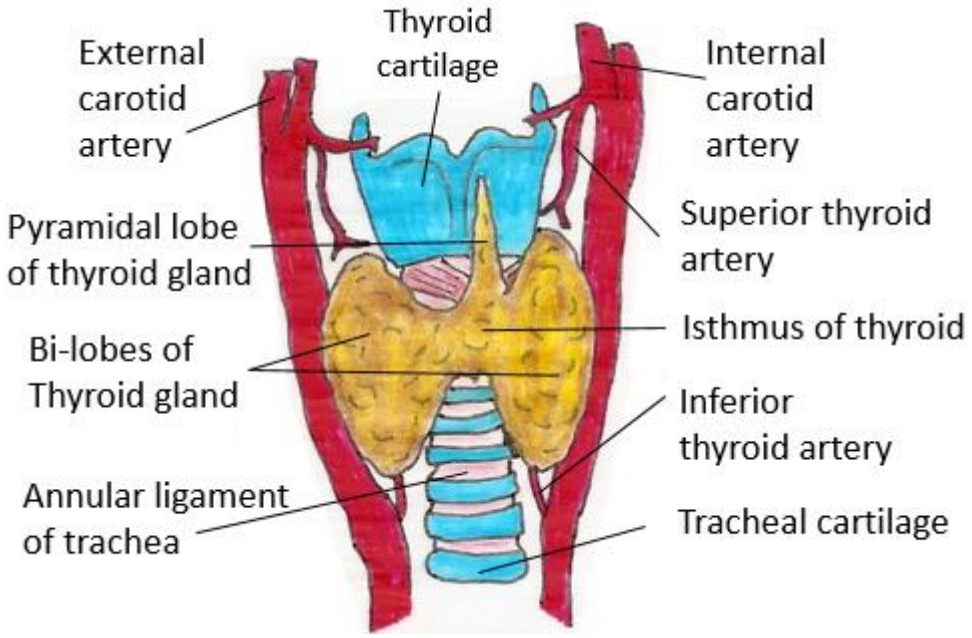


Figure 12.21 This drawing of the thyroid gland. It is relatively small gland that is shaped somewhat like a butterfly, located at the base of the front of your neck, just below the larynx or voice box. It has an excellent blood supply and the hormones produced by the thyroid gland, triiodothyronine (T^3) and thyroxine (T_4) have a tremendous influence on metabolism, thermogenesis and calcium ion (Ca^{2+}) levels in body fluids.

1) Thyroxine

The thyroid gland produces **thyroxine** (also called **T_4** because it contains 4 iodine atoms) and **triiodothyronine** (also called **T_3** because it contains 3 iodine atoms). Both T_4 and T_3 have similar effects on target cells, but the thyroid gland predominately makes T_4 (~80%) and in most target tissues the T_4 is converted to T_3.

Negative Feedback Loop Inhibition

Almost all hormones secreted by glands that are under the control of the hypothalamus are controlled by **a negative feedback loop**. When the hormone levels are high, they inhibit the hypothalamus and anterior pituitary, resulting in a decline in their levels.

These thyroid hormones are a perfect example of regulation by a ***negative feedback mechanism*** interaction with the hypothalamus and anterior pituitary gland as shown below in **Fig 12.22**.

Essentially this means that when there are sufficient thyroid hormones levels in the body, this inhibit the further production of them by the thyroid gland and inhibits stimulation of the thyroid by the hypothalamus.

Examine **Figure 12.20** below and note the sequence of events in a step wise manner:

1) Thyroid-releasing hormone (**TRH**) is released from the hypothalamus and travels to the anterior pituitary via the hypothalamic portal system;

2) This triggers the release of thyroid-stimulating hormone (**TSH**) from the anterior pituitary, which goes into the blood stream and travels to its target tissue the thyroid gland;

3) This causes the thyroid gland to release **T_3** and **T_4** hormones (making thyroxine) into the bloodstream;

4) As the thyroxine levels in the blood rise, it has an effect on all of its target tissues;

5) The final control of the loop is that the elevated thyroxine goes back to the hypothalamus and inhibits the further release of TRH, inhibiting further release of TSH and thereby decreasing thyroxine levels.

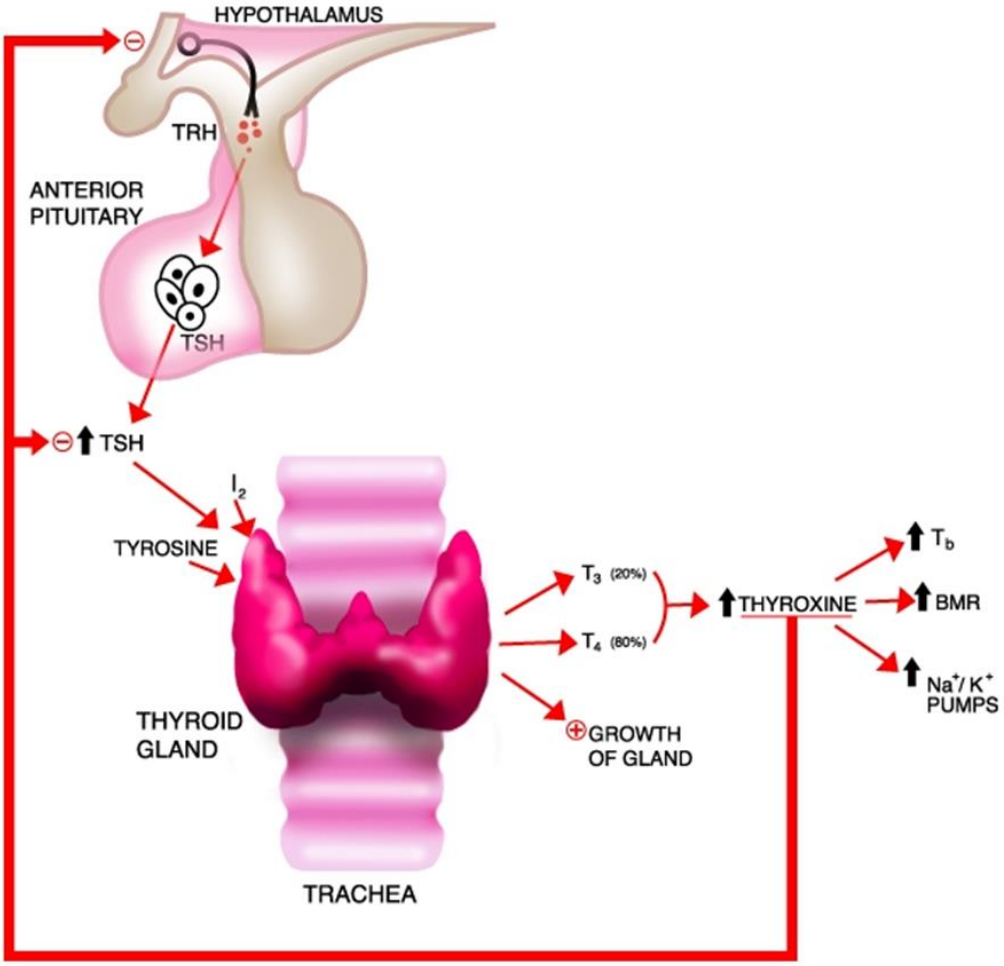


Figure 12.22 The drawing above (by a Miramar Physiology Student) shows the classic negative feedback control loop. The hypothalamus releases thyroid-releasing hormone (TRH) causing release of thyroid-stimulating hormone (TSH) from the anterior pituitary, this triggers the thyroid to release thyroxine, which when elevated inhibits the hypothalamus and the further release of TRH, inhibiting release of TSH and decreasing thyroxine levels.

Goiters of the Thyroid Gland

If the body lacks **iodine** (which you can only get from your diet), it cannot produce adequate amounts of the T_4 hormone for the appropriate conversion to T_3 to take place. When there are lower than normal thyroxine levels in the blood, this results in an excessive amount of thyroid stimulating hormone (**TSH**) being produced by the anterior pituitary.

Due to the constant stimulation of the thyroid gland by elevated TSH, it enlarges and as a consequence a **goiter** of the thyroid gland can result, yet it still can't make more T_3. It needs that iodine! A good dietary source of iodine is ocean fish and seaweeds like kelp.

Thyroxine is made by thyroid follicles in the thyroid gland (**Fig. 12.23**). This hormone is an important regulator of a person's **Basal Metabolic Rate** (BMR), that's like the idling speed of your body at rest and it's an indication of how much energy you require to sit and do nothing! This rate varies for everyone. Interestingly, during the cold months of winter the thyroid gland releases more thyroxine in an attempt to rev up your body and make you warmer. One of the ways thyroxine does this is to signal your cells to make more Na^+/K^+ pumps. These pumps are active transporters in all cells and use a lot of ATP to continuously pump Na^+ out and K^+ into your cells. As ATP is broken down (hydrolyzed) it releases heat energy (second law of thermodynamics) making you warmer. Thank you thyroid gland!

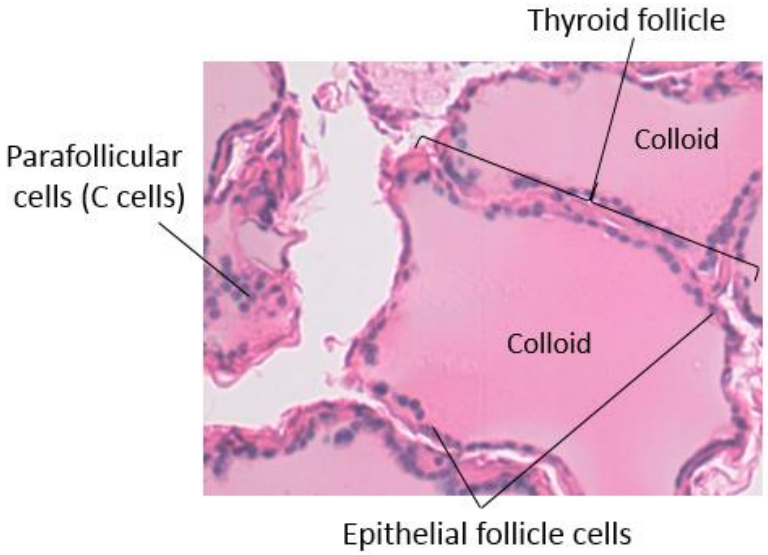


Figure 12.23 The histology of the thyroid gland seen here shows the thyroid follicles within the tissue, which contain colloid where T_4 and T_3 are made from glycoprotein attaching iodine to become thyroglobulin. The parafollicular cells (also called C cells) are where the hormone that reduces plasma Ca^{2+}, calcitonin is made.

Hypothyroidism occurs when the thyroid produce too little thyroxin. In adults this results in lethargy and weight gain. In infants, it causes cretinism, which is characterized by dwarfism, mental retardation, and lack of sexual maturity. Hashimoto's disease is an autoimmune disorder that involves the immune system attacking thyroid tissue, resulting in hypothyroidism.

Hyperthyroidism is when too much thyroxine (T_3 and T_4) is released; this increases heart rate and blood pressure, and causes weight loss. Graves' disease is another autoimmune disorder that causes the thyroid gland to produce excessive thyroid hormones, this is a common cause of hyperthyroidism.

2) Calcitonin

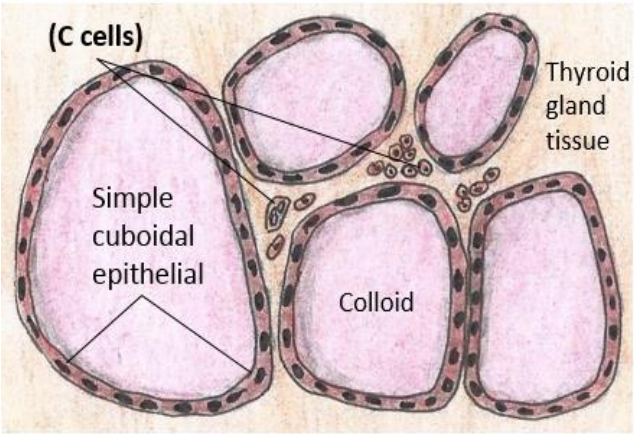


Figure 12.24 Drawing of thyroid follicles histology showing colloid (containing T_4 and T_3) and the parafollicular cells or C cells where calcitonin is made.

The thyroid gland also secretes the calcium (Ca^{2+}) regulating hormone **calcitonin**. Calcitonin is made by the **parafollicular cells**, or **C cells**. These are located outside of or 'next to' (para) the thyroid follicles in the thyroid gland. When Ca^{2+} levels in the blood are elevated, calcitonin is released to stimulate bone cells to deposit calcium into bone tissue. Bone is a dynamic tissue and functions as a storage site for important minerals such as Ca^{2+} and phosphorus. Bone cells called **osteoblasts** (literally meaning 'bone makers') are the cells stimulated by calcitonin to make more bone matrix and thus decrease the Ca^{2+} levels in the blood. Please note, the actions of calcitonin are *antagonistic* or opposite to those of the **parathyroid hormone**.

The Parathyroid Gland

There are actually are 4 small parathyroid glands that are embedded on the posterior surface of the thyroid gland. They secrete **parathyroid hormone** (PTH), which helps to control blood calcium (Ca^{2+}) levels in the body. When Ca^{2+} levels in the blood are too low, parathyroid hormone is released in order to elevate blood Ca^{2+} levels, and bone is the Ca^{2+} source that is tapped into.

A type of bone cell called **osteoclasts** (literally meaning 'bone destroyers') are stimulated to dissolve the bone matrix and thus release free Ca^{2+} from bone into the blood stream. The regulation of Ca^{2+} in body fluids is extremely important, not only for bones and teeth, but also for nerve functioning, muscle contractions, blood clotting and glandular secretion.

If we don't have enough calcium available for these functions, the body will take too much from the bones and cause them to decrease in mass and they may more easily fracture (e.g., osteoporosis). Too much calcium can cause kidney stones and weakening of muscle tone.

The Adrenal Gland

The adrenal glands sit on top of each kidney and hence are sometimes referred to as the *suprarenal* glands. The adrenal gland has two distinct anatomical and physiological portions that function as separate glands:

1) The outer **adrenal cortex**
2) The inner **adrenal medulla**

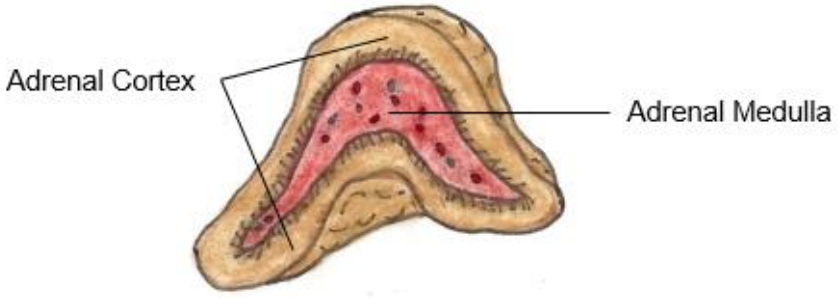


Figure 12.25 This drawing shows the adrenal gland. It is really two distinct endocrine glands in one. The outer portion is the adrenal cortex and releases 'cortical' hormones. The inner portion is called the adrenal medulla and releases epinephrine and

Both the adrenal cortex (outer portion) and adrenal medulla (inner portion) are influenced by the anterior pituitary as directed by the hypothalamus. The adrenal cortex is regulated by negative feedback involving adrenocorticotropic hormone (**ACTH**) and the medulla is regulated by nerve impulses from the hypothalamus.

1) The Adrenal Cortex

The adrenal cortex is divided into 3 different regions and each region produces a different type of hormone. The details of the spatial and histological arrangement is shown in **Fig. 12.25** above.

The adrenal cortex produces hormones that control salt balance in the blood (aldosterone), sugar balance (cortisol) and sexual development (androgens, estrogens). All of the cortical hormones are **steroids**. This means they are all derived from **cholesterol**!

The 3 Zones release 3 Types of Hormones from the Adrenal Cortex

The adrenal cortex is the outer region and also the largest part of an adrenal gland. ... The adrenal medulla is located inside the adrenal cortex in the center of an adrenal gland. It produces "stress hormones," including adrenaline.

1) Zona Glomerulosa – thin outermost portion, **Mineralocorticoids** made here, including ***Aldosterone***.

2) Zona Fasciculata – the thick, middle portion – the **Glucocorticoids** are made here, including ***Cortisol***.

3) Zona Reticularis – the inner, thin portion – the **Sex Steroids** are made here, including ***Androgens*.**

Keep in mind that the size of the adrenal gland is actually fairly small, about **½ inch** tall and about **3 inches** long, like a sort of groovy pyramid happily sitting atop the hard working kidneys. What will be apparent is that although very small, it is extremely complex. As shown by the three zones the drawing of the histology below (**Fig. 12.26**), the adrenal cortex (the outer portion) carries out three distinct functions in a very limited space. Hats off to the amazing adrenals.

The Histology of the Adrenal Gland

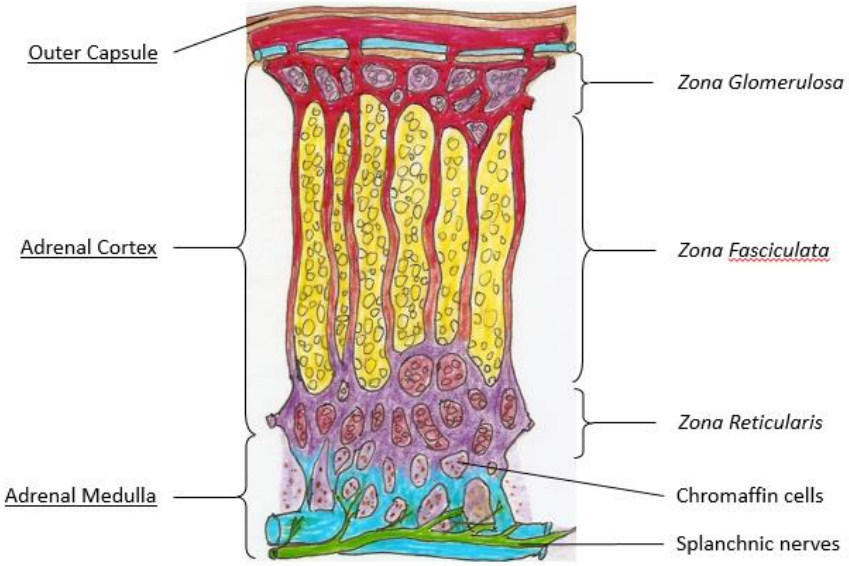


Figure 12.26 This is a drawing of the histology of the adrenal gland showing the three zones of the adrenal cortex, and the innermost region of the adrenal medulla.

The hormone **aldosterone** is released when the body is trying to conserve water, it acts by helping the kidneys to retain sodium in the body. The release of aldosterone is triggered by **angiotensin II** as a result of the renin-angiotensin-aldosterone system. Aldosterone acts to help maintain blood pressure and salt balance.

Increased sodium levels contribute to the retention of water and thus the increased blood volume in the body. In the absence of aldosterone, sodium is excreted and the lower sodium levels result in decreased blood volume and lower blood pressure.

The hormone **cortisol** has many vital roles in the body and it is also released in significant amounts in response to stress. Cortisol raises the level of glucose in the blood by stimulating the liver to produce

glucose from stored non-carbohydrate sources such as proteins and lipids and to release it into the blood. Cortisol acts as a natural anti-inflammatory agent by inhibiting the immune system and thereby reduces swelling.

It promotes **gluconeogenesis** – which means the body produces glucose from proteins and lipids in order to spare the use of glucose by most cells to ensure that cells like neurons (which can *only* use glucose) have enough in times of glucose scarcity. Gluconeogenesis can involve enhanced **lipolysis** and breakdown of skeletal muscle proteins. Cortisol is also needed for NE to have its vasoconstrictive effects. Many drugs are derived from cortisol to treat inflammation.

The steroid sex hormones **gonadocorticoids**, which include androgens hormones (male) and estrogens (female) are secreted in ***minimal*** amounts in both sexes by the **adrenal cortex**, but their effect is usually masked by the hormones released from the testes and ovaries.

Ultimately it is the hypothalamus and pituitary gland that control how much testosterone the testes produce and secrete, as well as the levels of estrogen and progesterone generated from the ovaries. The hypothalamus sends releasing hormones to the anterior pituitary gland to release the gonadotrophic substances **1)** follicle stimulating hormone (FSH) and **2)** luteinizing hormone (LH) as discussed in the earlier section covering the pituitary gland.

Hypothalamus-Pituitary-Adrenal Axis

Another excellent example of the highly regulated feedback loops in the endocrine system is the fine-tuned control of the hypothalamus-pituitary-adrenal axis seen in **Fig. 12.27 below.** The **hypothalamic-pituitary-adrenal (HPA) axis** describes the interaction between the hypothalamus, the anterior pituitary gland, and adrenal glands. This axis is a major component of and an excellent example of the homeostatic response involving **negative feedback loops**. There are feedback controls at every level of this system in order to be sensitive and responsive to the exact needs (whether real or perceived) of the body.

The main stimulus for the HPA axis is some kind of **stressor**. It can be a change in the circadian rhythms (or sleeping patterns); feelings of fear, anxiety or alarm; or from periods of extended hunger (e.g., from fasting). The HPA axis is dynamic and plays a vital role in regulating numerous physiological processes, such as metabolism, immune responses, and the autonomic nervous system (ANS).

Even before knowing what each of these hormones specifically does in the body, it is useful to note the pattern that is followed, just as it was for the thyroid gland in **Fig. 12.22** earlier. The step wise flow of events is provided below and can provide an overview for the familiar progression of communication.

Examine **Figure 12.27** below and again note the sequence of events in a step wise manner:

1) Corticotropin-releasing hormone (**CRH**) is released for the hypothalamus and travels to the anterior pituitary via the portal system;
2) This then causes the release adrenocorticotropic hormone (**ACTH**) from anterior pituitary;
3) The ACTH travels in the blood stream to the adrenal cortex and stimulates the release of **cortisol**;
4) As the cortisol levels in the blood rise, it has an effect on all of its target tissues;
5) The final control of the loop is that the elevated cortisol goes back to the hypothalamus and inhibits the further release of CRH, inhibiting further release of ACTH and thereby decreasing cortisol levels.

The Negative Feedback Loop of the Hypothalamus-Pituitary-Adrenal Axis

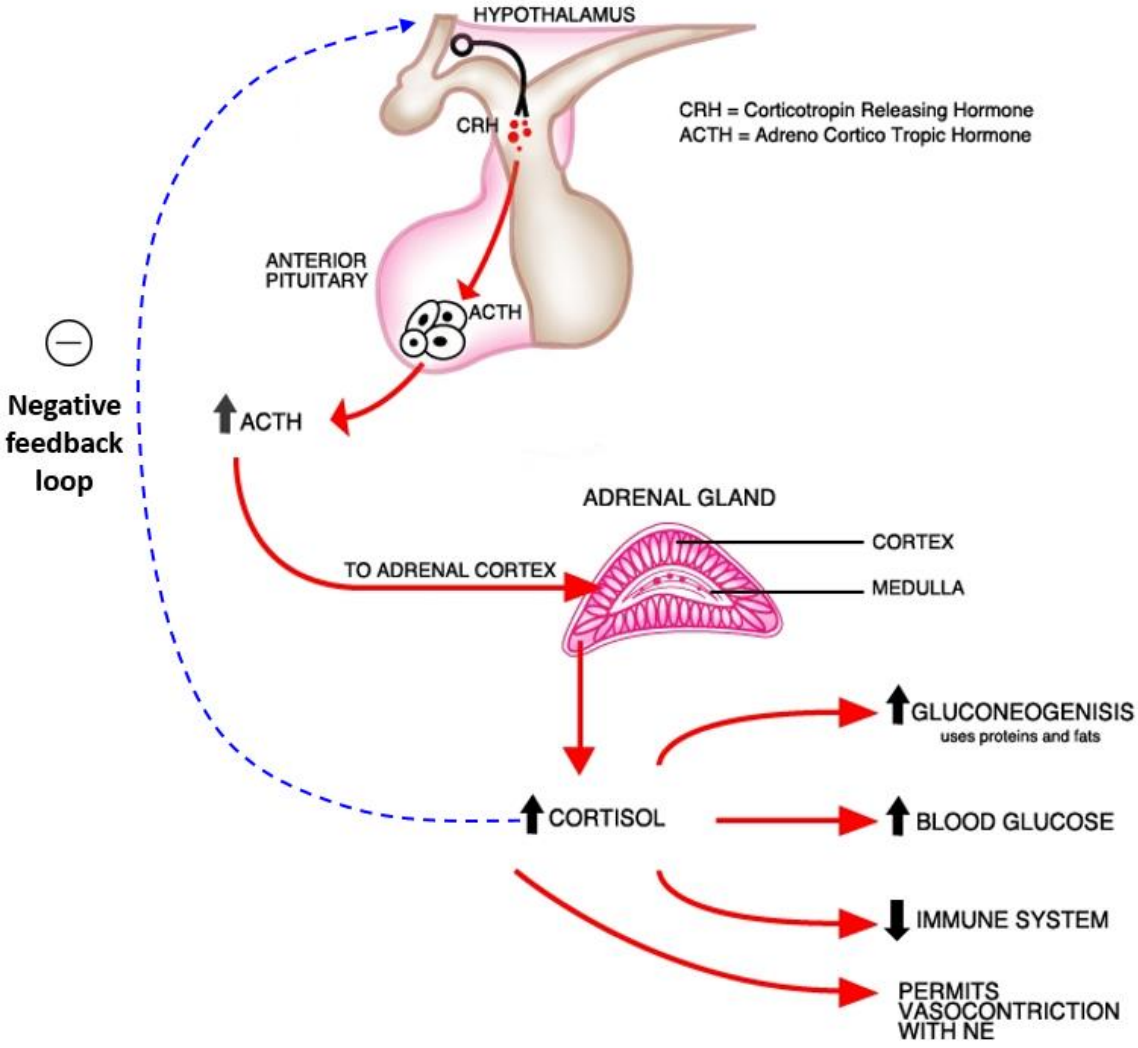


Figure 12.27 This shows the chain of command in terms of the signals that start at the hypothalamus. A change in circadian cycles or stress may cause the hypothalamus to release corticotropin releasing hormone (CRH), which travels to the anterior pituitary gland and promotes the release of adrenocorticotropic hormone (ACTH) which then goes to the adrenal cortex and promotes the growth of that gland, and the release of the hormone cortisol. Cortisol has a vast array of effects on the body, such as increasing blood glucose, suppressing the immune system, and enhancing vasoconstriction.

What does Cortisol do?

The hormone **cortisol** has many vital roles in the body and it is also released in significant amounts in response to stress. Cortisol **raises the level of glucose** in the blood by stimulating the liver to produce glucose from stored non-carbohydrate sources such as proteins and lipids and to release it into the blood. Cortisol acts as a natural anti-inflammatory agent by inhibiting the immune system and thereby reduces swelling. It promotes **gluconeogenesis** - which means the body produces glucose from proteins and lipids in order to spare the use of glucose by most cells to ensure that cells like neurons (which can *only* use glucose) have enough in times of glucose scarcity.

Gluconeogenesis involves enhanced **lipolysis** and an increased **proteolysis**, especially the breakdown of skeletal muscle proteins. This is why cortisol is said to be a glucose sparing molecule, as it promotes the

generation of glucose from non-carbohydrate sources., allowing any of the free glucose in blood to be utilized by neurons.

Cortisol works with norepinephrine (NE) to have a '**permissive effect**' in vasoconstriction. This effect is when one hormone, cortisol, enhances the effect of another hormone, NE, secreted later. Cortisol enables NE to act at its greatest potential as a more powerful vasoconstrictor. In states of ill health with low cortisol levels, blood pressure is also low because NE cannot act at its full potential.

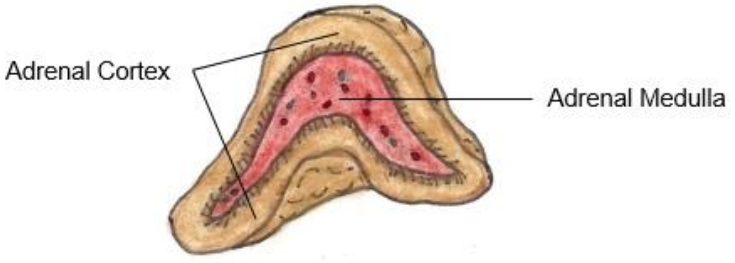
Cortisol helps to **inhibit defensive responses** and thereby **reduce inflammation**. Many drugs are derived from cortisol to treat inflammation because of this effect in the body (e.g., cortisone treatment).

In cases of **chronically elevated cortisol levels**, it tends to increase neuronal activity of the in the amygdala that are connected to fear. People under chronic stress may experience effects of exaggerated fear and anxiety in one part due to the prolonged elevated cortisol levels.

2) The Adrenal Medulla

The adrenal medulla is that inner portion of the adrenal gland (see drawing below). It can actually be viewed as a continuation of the nervous system, as it is composed of modified neural tissue. Therefore, it kind of makes sense that this 'gland' produces and secretes two catecholamine hormones that are also neurotransmitters in the CNS and PNS encountered earlier in chapter 8. The adrenal medulla makes **epinephrine** (**E**) and **norepinephrine** (**NE**), which used to be called adrenaline and noradrenalin, respectively.

The actions of epinephrine and norepinephrine have been covered previously and when released as hormones they in essence have the same effects. A variety of stressful conditions can stimulate the 'fight-or-flight' response of the sympathetic division of the autonomic nervous system (**ANS**) and it is directly wired to the **adrenal medulla** to release E (**80%**) and NE (**20%**) which act in concert with the sympathetic division of the ANS.



Chromaffin cells in the adrenal medulla are modified post-synaptic sympathetic neurons that receive sympathetic input and release E and NE into circulation. Hence they are called **neuroendocrine cells**. The effects of their release are the usual fight or flight responses - a faster heart rate, increased blood pressure and dilated airways to facilitate greater oxygen flow to the lungs. In addition, blood glucose levels are increased to make energy more available.

Predominantly, the secretion of E and NE is controlled by the hypothalamus via **sympathetic nerves** and not by pituitary hormones. The effects of this gland are fast and powerful because they are augmented by the coupling of the parallel sympathetic activity on the body.

The Pancreas

The pancreas is both an **exocrine** and an **endocrine** gland. It is nestled behind the stomach where its head is in close proximity to the **duodenum** of the **small intestine**. The exocrine portion makes 'pancreatic juices' (in the pancreatic acini) which are digestive enzymes used in the digestive system to break down and absorb nutrients. The **endocrine** portion of this gland is contained in the **pancreatic islets** (islets of Langerhans) and makes 2 hormones that regulate blood glucose levels: **1) Insulin** and **2) Glucagon**. Below in **Fig. 12.28** the pancreas is shown in relation to its proximity to the small intestine and the gallbladder.

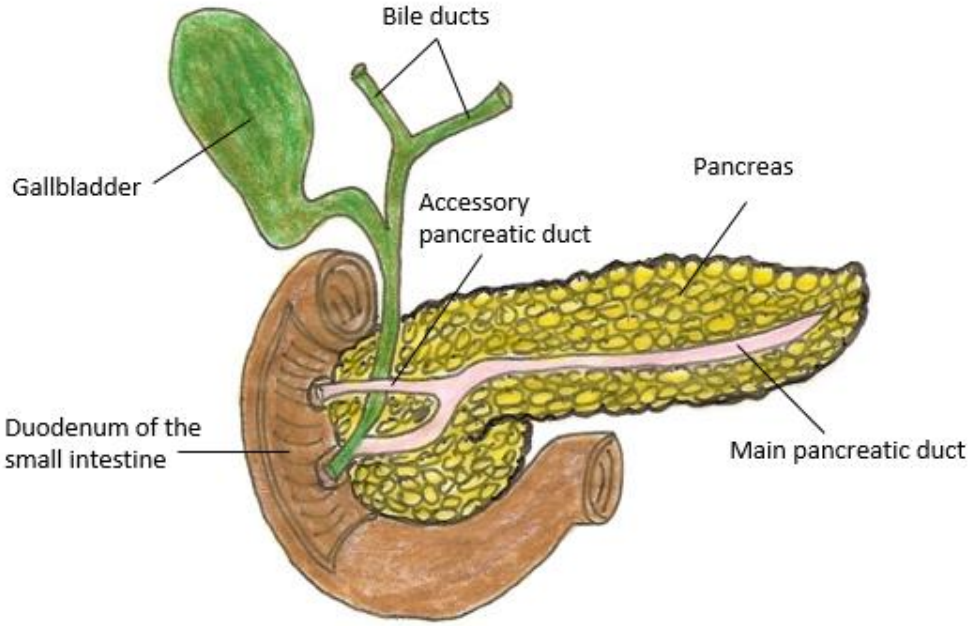


Figure 12.28 This is a showing the important arrangement of the gallbladder, the pancreas and the duodenum of the small intestine. The gallbladder stores and concentrate bile made by the hepatocytes of the liver. The pancreas in its exocrine role makes pancreatic juices which are powerful digestive enzymes. In its endocrine role, the pancreas makes several hormones that regulate the metabolism of glucose, including insulin and glucagon.

1) Insulin

The role of insulin is to lower elevated blood glucose levels after a meal, and bring it back to the baseline values, which are different for everyone but range from **70 to 110 mg/dL**. When your blood glucose concentrations are elevated above the normal range, the beta (**β**) cells in the pancreatic islets (or islets of Langerhans) secrete the peptide hormone insulin. Insulin flowing through the blood stream signals target cells to insert **glucose transporters** into their plasma membranes, this way they can take up the excess glucose that is circulating in the blood.

Thus, insulin promotes the removal of the additional glucose from the blood so it can be stored as **glycogen** in the liver and skeletal muscle, this process is called **glycogenesis**, meaning making glycogen. Insulin also promotes many other **anabolic** activities such **lipogenesis**, which means making fat, so this hormone stimulates the storage of adipose (fats) in adipocytes (fat cells). It also stimulates **protein synthesis** in skeletal muscle. Both the protein and fat synthesis occurs through the **tyrosine kinase** receptor pathway in these tissues.

Immediately after a meal:

After eating a typical meal that contains carbohydrates, the digestion of it will result in an increase in blood glucose. The numbered diagram below in **Fig. 12.29** goes through this step by step. This increase in blood glucose will be detected by **beta cells** in the pancreatic islets and they will release **insulin** into the bloodstream ① in response to this. Insulin has the ability to affect almost every type of cell in the body. At the target cells, insulin binds to receptors ② on the plasma membrane and triggers the cells to insert **GLUT 4** and **GLUT 8** transporters into their plasma membranes. The GLUT 4 transporter is a protein carrier for glucose that the majority of cells in the body contain. Once the GLUT 4 transported is in the plasma membrane, all glucose has to do is bind to the carrier protein, take a little spin through the membrane as the glucose moves **down its concertation gradient** into the cell. Remember from section one that this is **facilitated diffusion** of glucose. By transporting the glucose from where it is high in the ECF (plasma and interstitium) to where it is low in the ICF ③, it lowers the glucose levels in the blood. This decrease in blood glucose is detected by the pancreatic islets cells and the beta cells stop releasing insulin, since their job of lowering blood glucose back into its normal range is done!

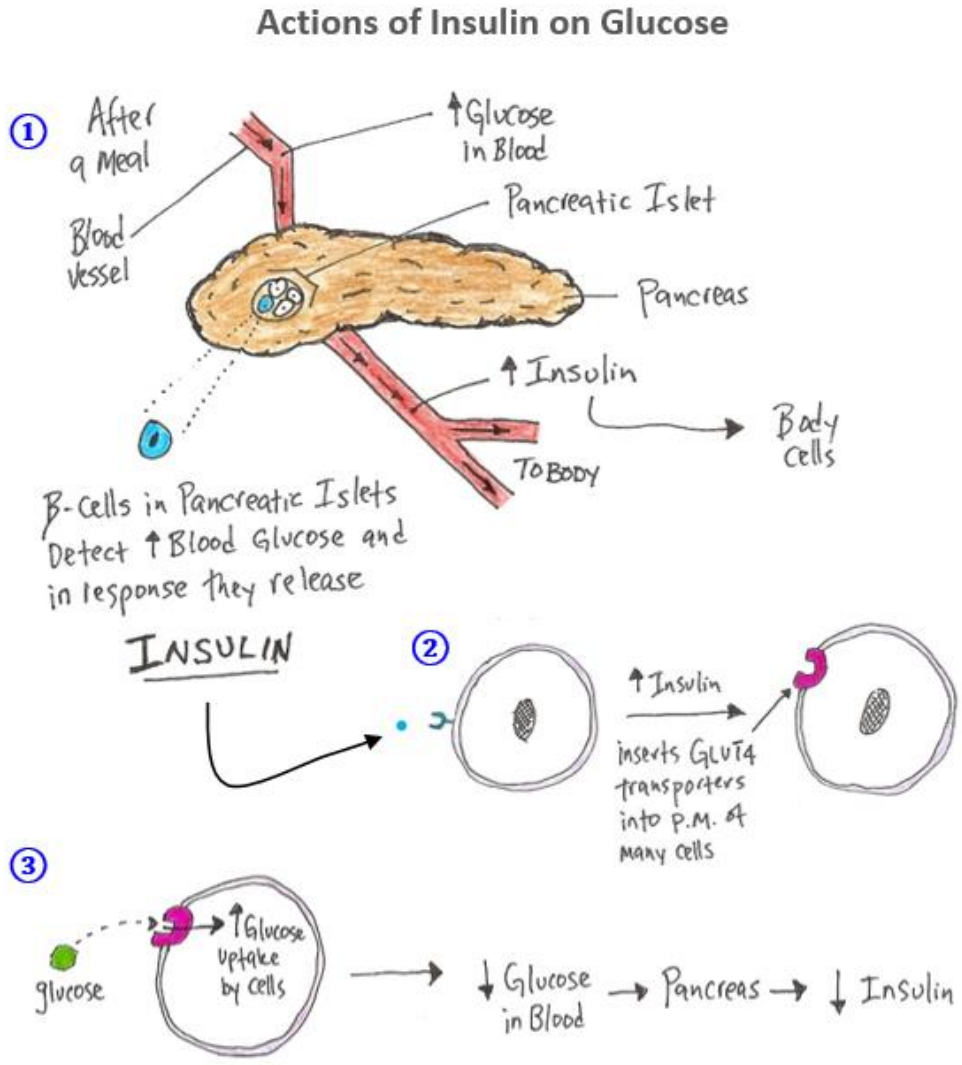


Figure 12.29 Shown here is a feedback loop for elevated blood glucose after a meal. This increase ① is detected by beta cells in the pancreas, triggering release of insulin into the bloodstream. Insulin binds to receptors ② on the plasma membrane of many cells, activating them to insert GLUT 4 transporters into their plasma membranes. The high glucose in the blood moves down its concentration gradient by facilitated diffusion into the cells ③. This causes a reduction in blood glucose levels, which is detected by the pancreas and the beta cells stop releasing insulin.

How GLUT 4 Transporters Increase in the Cell's Plasma Membrane

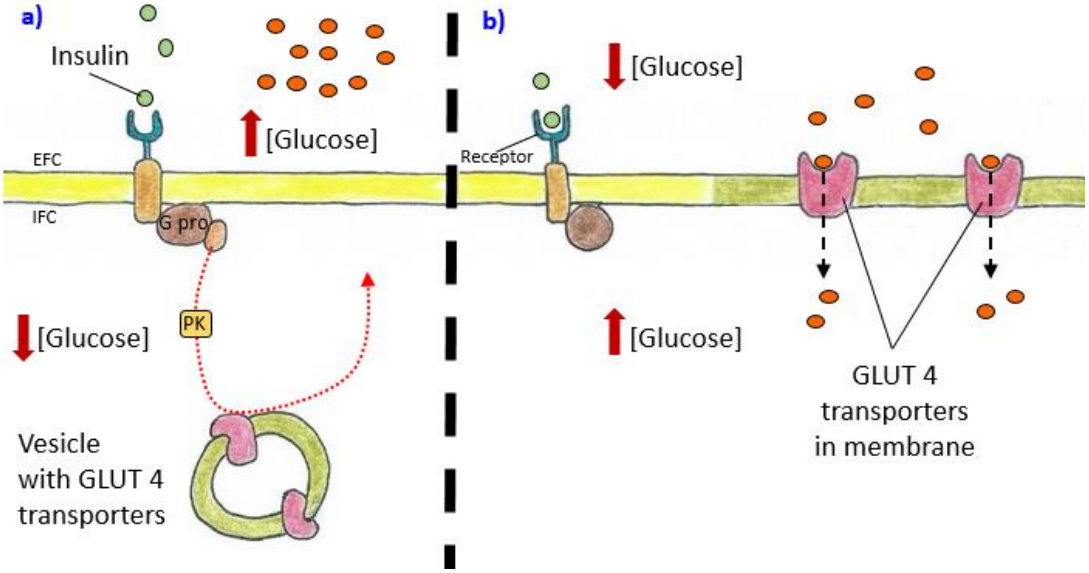


Figure 12.30 When insulin binds **a)** to membrane receptors, it triggers a second messenger system that phosphorylates vesicles containing GLUT 4 transporter to fuse with the plasma membrane. This inserts GLUT 4 transporters into the plasma membrane **b)** where they can transport glucose into cells from the blood plasma (via facilitated diffusion) which rapidly decrease blood glucose levels.

If the pancreas fails to produce enough insulin (type 1) or the body becomes desensitized to insulin (type 2), the result can be **diabetes mellitus**. Note that most neurons in the brain and spinal cord do not require insulin in order to use glucose. In addition, skeletal muscle when contracting during exercising can use insulin independent glucose transporters, thus exercise lowers blood glucose without requiring insulin.

Once **blood glucose levels** have been decreased and are back into the normal metabolic range, the signal to the pancreas to release insulin is no longer present, thus insulin stops being released into the blood stream. In other words, this operates on a negative feedback loop system.

What does the Glycemic Index Represent?

The **Glycemic Index** (GI) is a system of assigning a number to foods that contain carbohydrates, according to how much and how quickly each food increases blood glucose levels. It indicates how quickly a certain food turns into glucose in a person's body. Foods are ranked on a scale of 0 to 100. The **Glycemic Load** (GL) indicates the total amount of glucose in the food. See the example comparisons to the right.

Glycemic Load =
Glycemic Index x Carbohydrates/100.

Different categories of foods will yield different blood glucose levels. **Fig. 12.31** below shows a comparison between the 3 main food groups: Carbohydrates (simple and complex); Proteins; and Fats (Lipids). It will depend on the exact nature of the food, however, the general pattern shows that simple carbs (e.g. refined sugar) makes blood glucose peak the fastest, whereas Fats give the slowest rise in blood glucose.

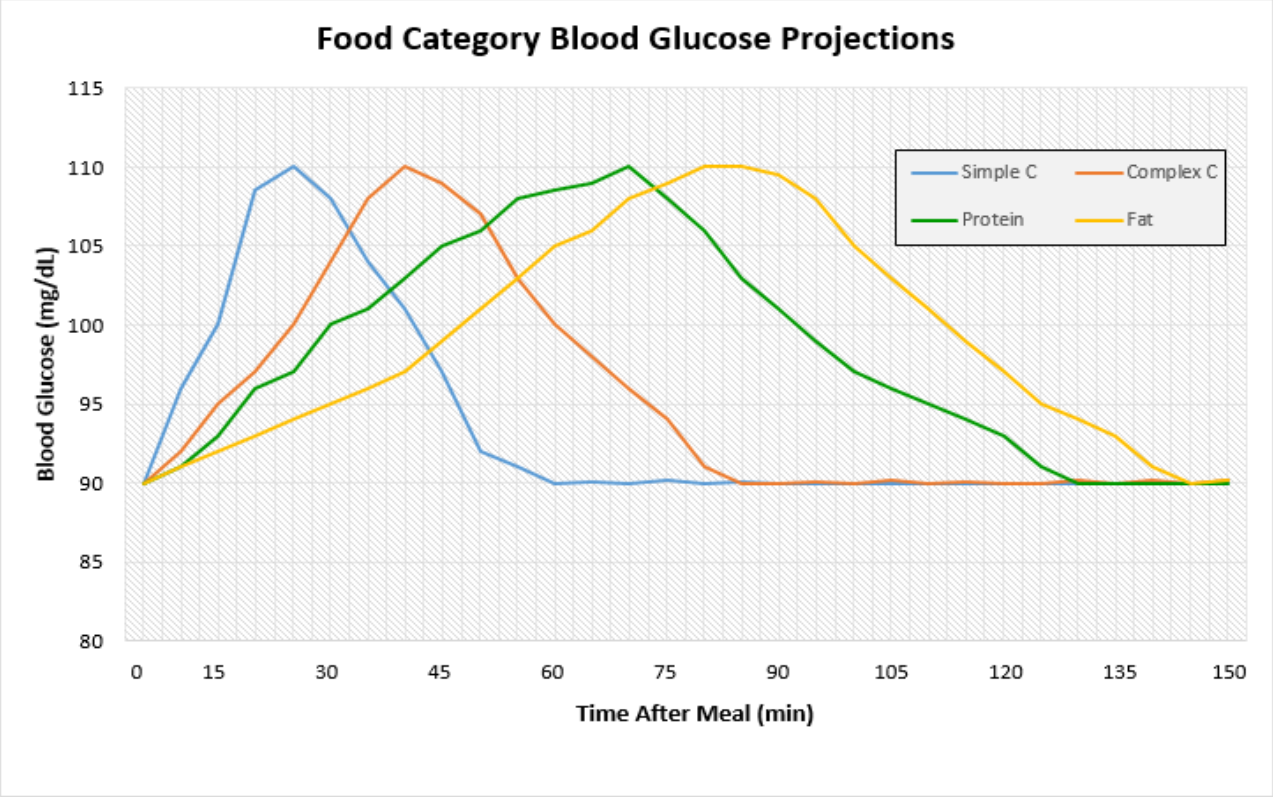


Figure 12.31 The glycemic index is a measure of how different foods affect blood glucose levels. Examples of blood glucose levels after a meal of simple carbohydrates (Simple C) complex carbohydrates (Complex C), proteins (Proteins) and fats (Fats). Notice the variation in the peaks and spans of glucose levels in the blood between the different food groups.

2) Glucagon

The alpha (**α**) cells in the pancreatic islets secrete glucagon in response to low concentrations of glucose in the blood, so its actions are *antagonistic* or the opposite of insulin. It is normally secreted between meals to maintain stable concentration of glucose in the blood. Glucagon causes the liver to hydrolyze its glycogen stores into glucose and release it into the blood stream, thereby increasing blood glucose levels. It also causes fats and proteins to be converted into glucose, a process called **gluconeogenesis**, as well as other **catabolic** activities.

<u>In between meals</u>:

If a person has not eaten in a while, the body will use the glucose in the blood and these levels will begin to decrease. The sequence of events that glucagon instigates as a remedy to any decrease in blood glucose levels is shown in a step by step manner in **Fig. 12.32** below. In between meals, if blood glucose starts to decrease below about 70 mg/dL this is detected by **alpha cells** in the pancreatic islets ①. They will release the peptide hormone **glucagon** into the bloodstream in response to this ②. Glucagon first and primarily goes to the **liver** and stimulates the release the glucose stores that reside there in the form of **glycogen** by a process called **glycogenolysis**, which means the breaking down glycogen) ③. The **hepatocytes** of the liver release this glucose into the bloodstream, increasing blood glucose. In addition to this, glucagon also

promotes the actions of **gluconeogenesis** in the liver cells, which is a way of making glucose from non-carbohydrate sources, such as **lipids** and **proteins**. The term gluconeogenesis translates into "sugar new make". The net result is a release of stored glucose sources into the blood that elevates blood glucose.

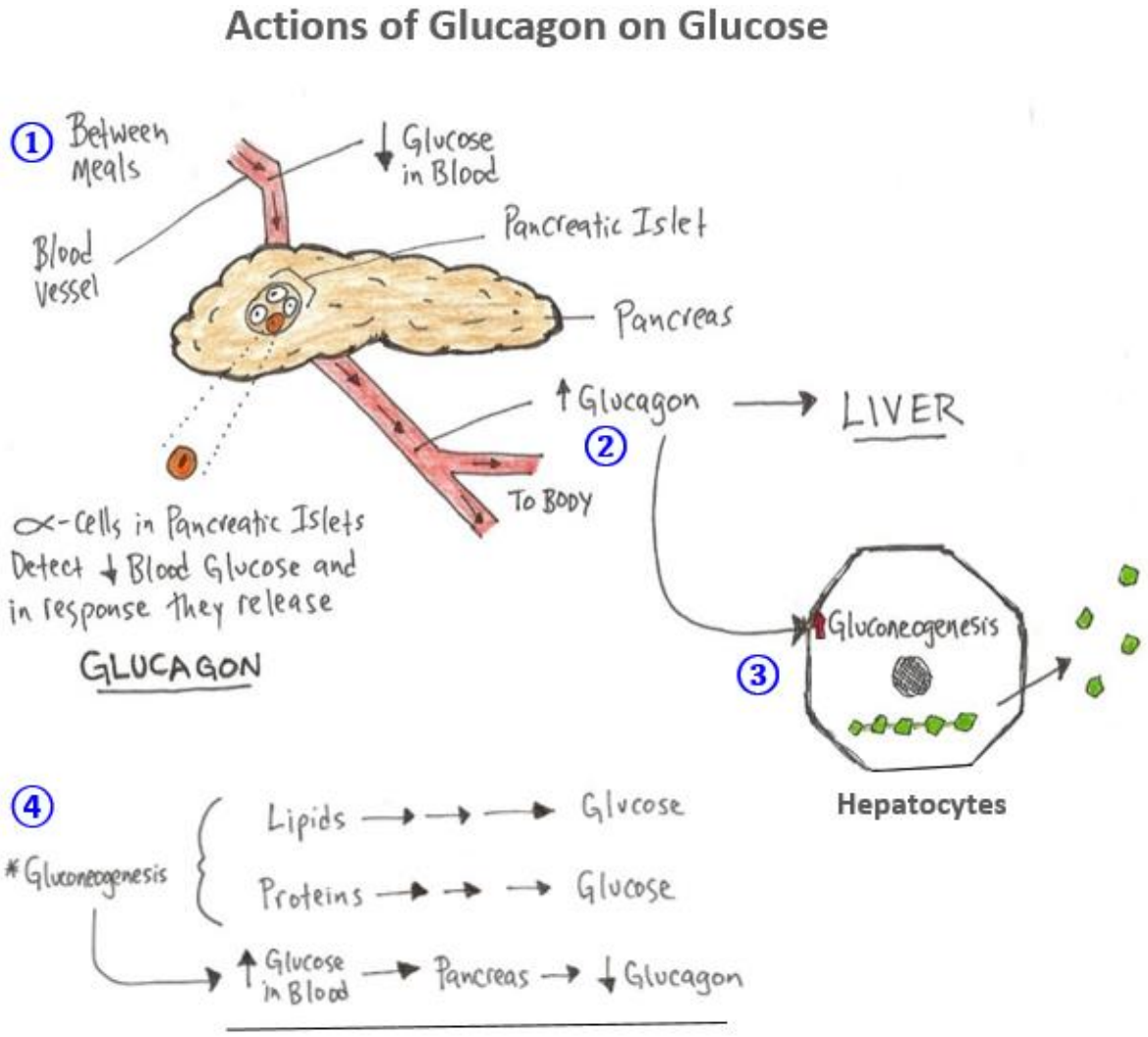


Figure 12.32 Shown here is a feedback loop for decreased blood glucose in between meals. This decrease ① is detected by alpha cells in the pancreas, triggering release ② of glucagon into the bloodstream, which primarily stimulate the ③ hepatocytes of the liver to engage in glycogenolysis and gluconeogenesis, yielding free glucose delivered into the bloodstream. The gluconeogenesis ④ is a mechanism of making glucose from lipids and proteins which has a 'glucose-sparing' effect, saving the glucose present for the neurons. The increase in blood glucose levels trigger the pancreatic alpha cells to stop releasing glucagon, as their job of elevating blood glucose back up into its normal range is done.

The Glucose-Sparing Effect

When the process of gluconeogenesis is occurring it liberates glycerol, fatty acids and amino acids to be used by the body. Glycerol can be used to make glucose, or used in glycolysis. **Glucagon** and **epinephrine** trigger lipolysis, and the fatty acids generated by this can be further catabolized by many cells, especially in aerobic muscle fibers. In addition, a direct action of **growth hormone** is to stimulate fat breakdown (lipolysis again) and release fatty acids into the blood stream. This triggers a switch in most tissues from utilizing glucose as an energy source to utilizing **fatty acids** as an energy source.

This process of using non-carbohydrates as a type of substitute for glucose is called "**the glucose sparing effect**", because it provides alternative sources for various cells that can use them, but this allows more glucose to be available for those cells like **neurons** that rely exclusively on glucose.

Somatostatin

The pancreas also produces the hormone **somatostatin**. Like insulin and glucagon, it is made in the islets of Langerhans but by the **delta** cells that are present there (see below). In the pancreas, the role of somatostatin is to block the secretion of both insulin and glucagon from adjacent cells in order to regulate the flow of nutrients into and out of the circulation. See pancreatic islet to the right with delta cell releasing somatostatin. From its name, soma (or somato) = body; and statin = stasis, or stopping; this indicates that somatostatin stops growth in the body.

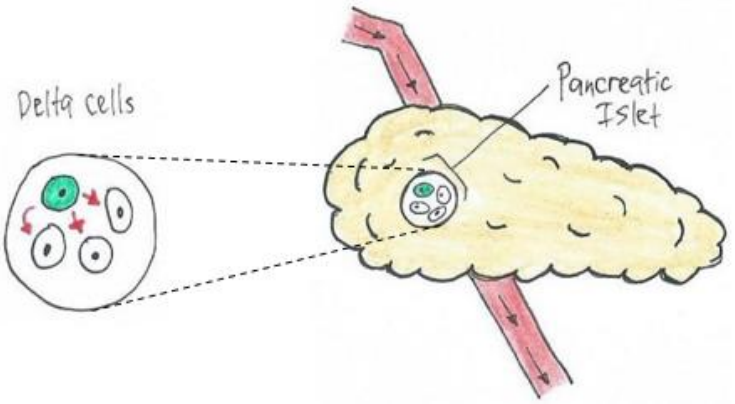


Figure 12.33 The pancreatic islets also contain delta cells that release somatostatin which inhibits the secretion of the other pancreatic hormones, including insulin and glucagon.

Somatostatin acts in contrast to **Somatotropin** hormone, which is also called **Growth Hormone** (made by the anterior pituitary gland), which promotes growth.

Somatostatin is also released elsewhere in the body. The hypothalamus releases somatostatin in order to inhibit the pituitary gland's secretion of **Growth Hormone** (GH) and **Thyroid Stimulating Hormone** (TSH), thus it is an inhibiting hormone of the hypothalamus. Also, in the gastrointestinal tract, somatostatin **reduces gastric secretion** and inhibits the emission of the gastrointestinal hormones **secretin** and **gastrin**.

Diabetes Mellitus

Diabetes Mellitus is a disease in which glucose cannot be sufficiently metabolized by the body, such that a person has high blood glucose but cannot use this glucose that is in the blood. The term for elevated glucose levels in the blood is ***hyperglycemia*** (emia = blood) and glucose in the urine is called ***glycosuria*** (uria = urine). In this situation, cells can starve because glucose is not being metabolized, even though there is an excess of glucose in the blood. [*See section in Blood and Endocrine DM discussion*]

The Secondary Endocrine Glands

As mentioned at the beginning of this section, there are many organs and glands that are secondary endocrine glands because their primary function is not as an endocrine gland, however secondarily they releases hormones, and so these structures are integrated within the endocrine system.

The Heart

The heart is an amazing organ for the cardiovascular system, but it is also a secondary endocrine gland because it produces hormones, two of which are **atrial natriuretic peptide** (**ANP**) or factor (**ANF**), and **brain natriuretic peptide** (**BNP**). A nice summary of the stimulation and release of ANP and BNP from the heart is seen in **Figure 12.34** below.

ANP is a 28-amino acid peptide synthesized and released by **atrial myocardiocytes** in response to atrial distension (elevated blood volume). For atrial natriuretic peptide, it name indicates its function. It is made in the superior chambers of heart called the atrial; the natri- part means sodium (Na^+); and the uretic part means relating to or occurring in the urine. This hormone makes the renal system get eliminate of more sodium in the urine.

How are the atria triggered to release ANP? The atrial myocardiocytes have **mechanoreceptors** that are stimulated when the tissue is stretched and this occurs when there is an increase in atrial blood volume. This stretching of the atrial walls triggers the release of ANP. The ANP travels in the bloodstream to the kidneys diminishes the release of renin. This decreases the release of both ADH and aldosterone. In this way there is an increase in the excretion of Na^+ and water in the renal system. The action of increasing sodium excretion is called **natriuresis**, and the action of an increase in fluid excretion from the body via urine id called **diuresis**. By doing this, there is a reduction in the extracellular fluid (ECF) volume in the body, and this lowers systemic blood pressure.

ANP is also a powerful **vasodilator** which acts to lower blood pressure. The release of **ANP inhibits renin** secretion from the kidneys, thereby inhibiting the renin-angiotensin-aldosterone system that acts to conserve water. Its release is primarily triggered in response to high blood pressure.

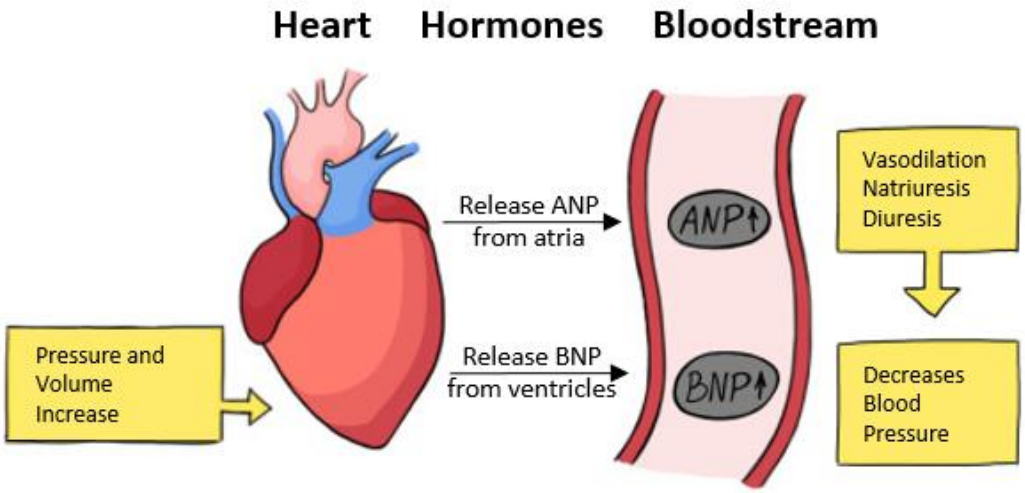


Figure 12.34 If there is an increased in pressure and volume in the atria (top two chambers) of the heart, it releases atrial natriuretic peptide (ANP) is released, and an increased in pressure and volume in the ventricle (bottom two chambers), brain natriuretic peptide (BNP) is released. Both ANP and BNP cause natriuresis, diuresis and vasodilation that reduce blood pressure.

Despite brain in its name, BNP, is not made in the brain but by myocardiocytes in the **ventricles** of the heart. It has actions and effects that are similar to ANP, though it actions are is less intense with a shorter half-life so the effects diminish more quickly than for ANP.

In Summary: These two cardiac hormones, ANP and BNP, **lower blood pressure**. In essence they do so by inhibiting the release of the renal hormone **renin** and the adrenal hormone **aldosterone** (which normally act to conserve water and Na^+ in the body). In addition, ANP and BNP both promote vasodilation in arterioles, which lowers blood pressure.

The Thymus

The thymus is part of the immune system as well as being an endocrine gland. It is an important lymphoid organ as its role in the lymphatic system is covered in detail in that section.

The thymus sits comfortably above anterior aspect of the heart directly behind the sternum (breastbone), it has two lobes that join in front of the trachea (see **Fig. 12.35** below). Each lobe is made of lymphoid tissue, consisting of tightly packed white blood cells and fat. Its function is to transform **lymphocytes** (a type of white blood cells) into **T-cells**. In fact, the name *T-cell* denotes that they develop and mature in the Thymus! The T-cells are then transported to various lymphoid glands and tissues where they play an important part in fighting infections and disease and also guard against abnormal cell growth, as in cancer, and any foreign tissues that gets into our bodies.

The thymus releases a hormone called **thymosin**, which is a polypeptide hormone that increases the activity of T-lymphocytes. Swelling of lymph glands and fever are signals that immune cells are multiplying to fight off invaders of the body.

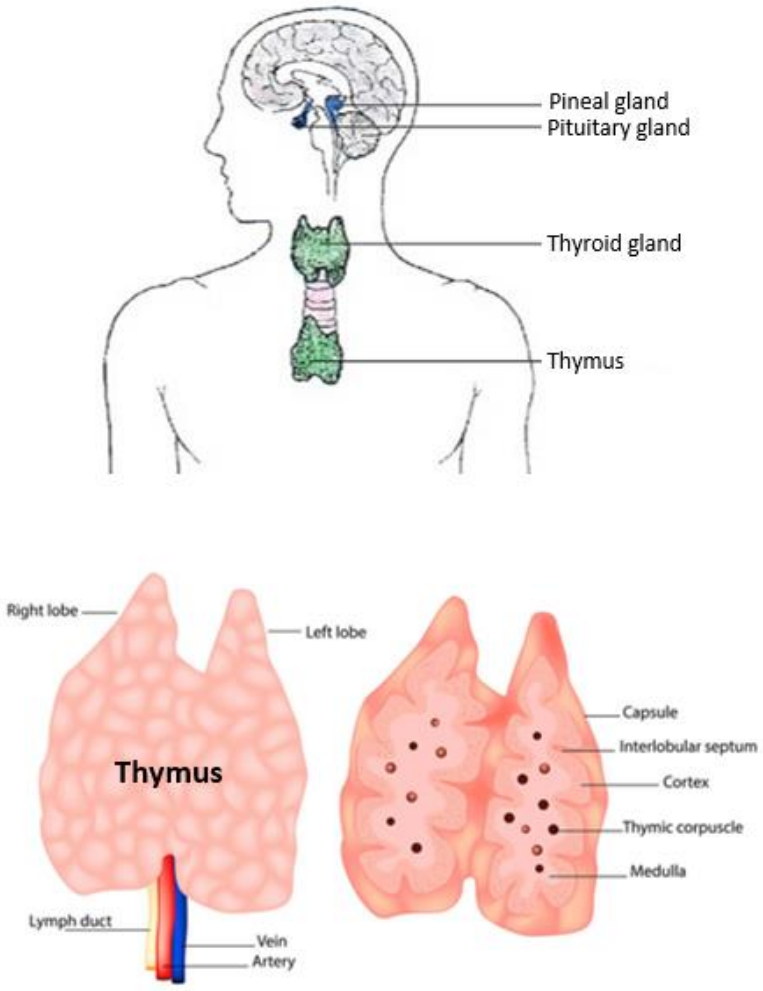


Figure 12.35 The location of the thymus gland in the body is in the thoracic cavity on top of the heart and between the lungs. Seen below is a view of it at the tissue level. The thymus plays a role in the differentiation of T lymphocytes (or T-cells) before adulthood.

Early in life the thymus enlarges significantly until puberty. Based on cadaver studies, medical institutions contend that the thymus gland atrophies (gets smaller) into adulthood and turns into adipose and fibrous tissue as we age, a process called involution. However, many other studies show that a healthy thymus should remain large and robust throughout life.

A key to a happy and healthy thymus is adequate vitamins, minerals, exercise, eating un-processed (organic) whole foods and avoiding unhealthy refined foods and toxins. But this is a remedy for most things. Additionally, aggressive anti-nutrients such as any unfermented soy, high fructose corn syrup, aspartame and Splenda, MSG, trans-fats, artificial colors and artificial flavors. Many research studies have shown that coconut oil is very beneficial to the human body. It is a saturated fat, not a trans-fat. Despite the well promoted notion that 'saturated fats are bad and cause heart disease' this is ***not true*** but still widely and erroneously believed.

The Female and Male Gonads

Gonads are the primary reproductive organ in humans; in females they are the **ovaries** and in males they are the **testes**. The gonads produce **gametes** or the ***sex cells*** for reproduction; in females the ovaries make **egg cells** (or oocytes) and in males the testes make **sperm cells**. The gonads also produce the **sex hormones**; in females the ovaries make **estrogen** and **progesterone** and in males the testes make **testosterone**.

Secondary Sexual Characteristics

The **sex hormones** are responsible for the development of secondary sexual characteristics, which predominantly develop at puberty. Some secondary sexual characteristics in females are development of the breasts and broadening of the pelvis (birth canal). Examples in males are the deepening of the voice (due to a larger larynx), growth of facial hair, thickening of many boney structures and greater skeletal muscle development. During puberty, both sexes have increased activity of sweat glands and sebaceous glands (oil glands in the skin), and growth of pubic and axillary (armpit) hair.

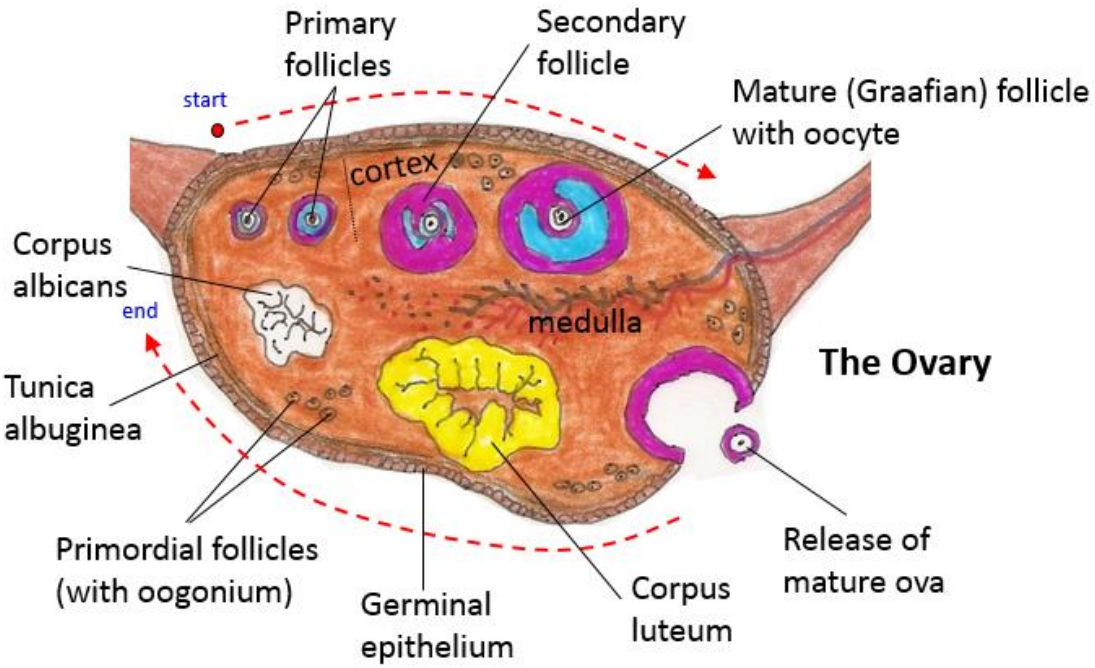


Figure 12.36 Shown above is the ovarian cycle from the start (top left), with the developing eggs enclosed in primordial and primary follicles, to release of the mature ova from the mature follicle at ovulation, to the presence of the corpus luteum and to the end with the formation and disintegration of the corpus albicans.

The Ovaries

The oval-shaped **ovaries** flank either side of the uterus in females and release an egg or "ova," each month. The ovaries also release the female sex hormones **estrogen** and **progesterone**. The **ovarian cycle** is like a remarkably complex clock, with a multifaceted set of events occurring in parallel and in sequence as depicted in **Figure 12.36** above. This cycle within the ovaries is dictated by the release of **LH** and **FSH** from the anterior pituitary gland. The ovary then in turn dictates the patterns of the **uterine cycle** which involves changes in progesterone and estrogen levels that are responsible for many changes, including the sloughing off of the inner endometrial layer of the uterus every month during the female **menstrual cycle**.

A female is born with about **1 to 2 million cells** that all have the potential to develop into mature reproductive cells. These cells are housed in follicles that go through various stages of development within the ovary. This number diminishes to approximately **300,00** to **500,000** cells at puberty. Roughly only about **400** of these will ever fully develop during the woman's lifetime.

The estrogen and progesterone made by ovarian structures such as the **corpus luteum**, are responsible for regulating the uterine cycle and for the obvious secondary sexual characteristics of females, like growth of mammary glands, widening of pelvis, and distribution of fat and muscle mass. At the end of the uterine cycle, if pregnancy does not occur, the corpus luteum becomes the **corpus albicans** (see **Fig. 12.36**).

Structures of the Ovaries Producing Hormones

1) It is the **ovarian follicles** in the ovary that synthesize and secrete the female steroid sex hormones that play vital roles in female development. These follicles produced the three major classes of female sex hormones: **Estrogens**, **progestins**, and **androgens**. The role of these hormones is elaborated in the female reproductive section (see chapter 23).

2) After ovulation, the ovarian follicle becomes the **corpus luteum**, it is the corpus luteum that produces the hormones **estrogen** and **progesterone** after the middle of the ovarian cycle. It is the production of progesterone that is a central function of the corpus luteum. The increase in progesterone after ovulation changes the uterus into a healthy environment for a fetus to develop and grow.

If implantation occurs the corpus luteum is maintained. If implantation does not occur, then corpus luteum (‘yellow body’) will be transform into the corpus albicans (‘white body’), which signals menstruation to commence. The corpus albicans is degraded by resident macrophages and re-incorporated as the ovaian cycle is repeated.

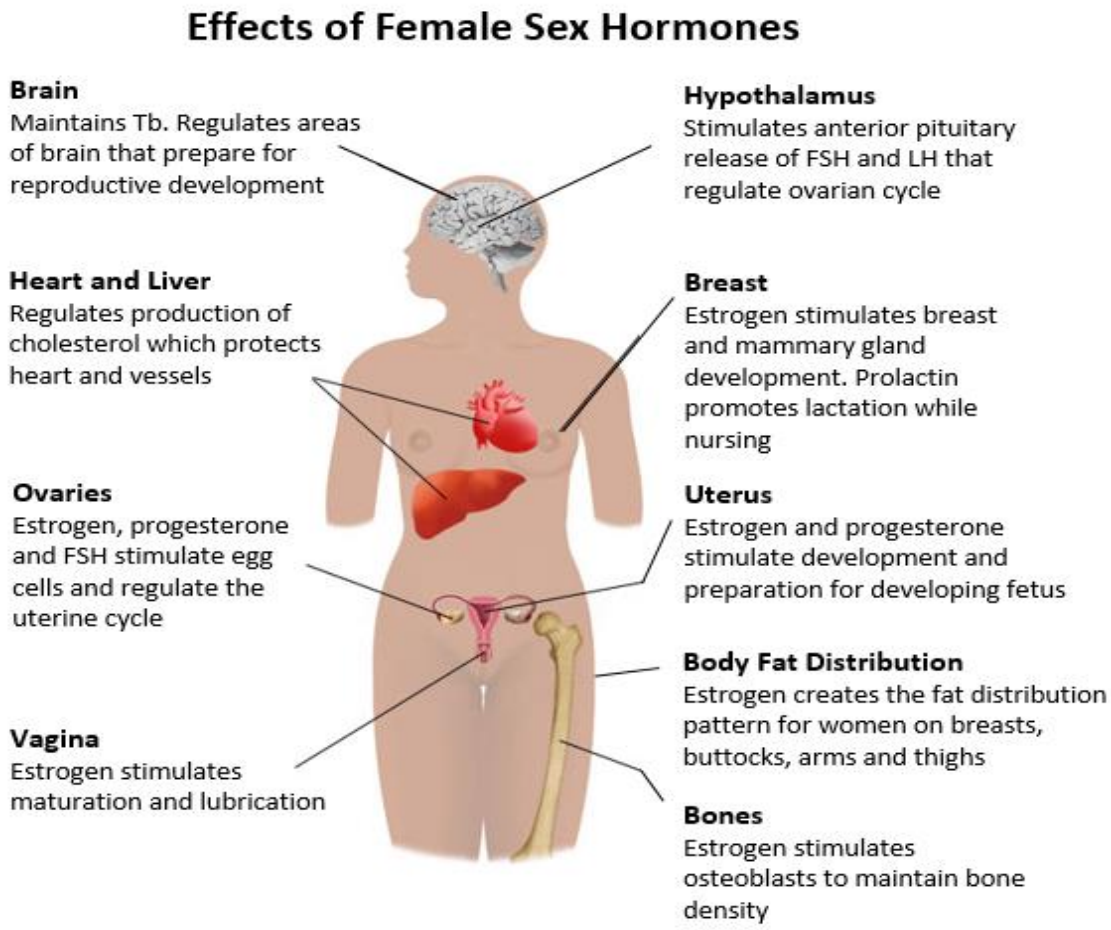


Figure 12.37 Shows the effects of the female sex hormones on the female body. It is chiefly estrogen that causes many of the secondary sexual characteristics for females, but progesterone is also involved, as are follicular stimulating hormone (FSH), luteinizing hormone (LH) and prolactin (PRL).

Female Secondary Sexual Characteristics

For females, the secondary sexual characteristics are those elements and structures of the body that pertain to the physiological functions that then result in the physical traits of being female. These include having relatively very little body hair, but also in some cases thicker hair on the head. The skeletal structures of the pelvis are very different for women and men, as the female pelvic outlet must be much more broad and open to accommodate the birth of a baby, as this region is an integral part of the birth canal. As a consequence of that, females have a broader hips-to-shoulder ratio than males.

The more rounded and shapely figure of females is due to **subcutaneous fat** storage, compared to males who predominantly store excess fat as **visceral fat** padding internal organs within the abdomen, this can also be called belly fat, or a pot-belly. It is predominantly **estrogen** that causes a typical fat distribution pattern in females. This includes fat storage in the **breasts**, **buttock region**, **upper arms** and **thighs**. During the reproductive years, women get additional fat deposition in the pelvis, buttocks, thighs, upper arms and the breasts to provide an energy source for potential pregnancy and lactation.

For females, the 'hips' are actually located about where the palms of the hands of a woman rest at her side as seen in **Fig. 12.38** below. This is naturally the widest part of the female body, regardless of body weight. Compared to males, females have a decreased ability to generate muscle mass at a fast rate,

decreased upper body strength and a gait that involves a swerving of the legs out and then in-line, one in front of the other. Men extend their legs forward like a toy soldier would walk. This is due to the different quadriceps or **Q angle** that is much large in women.

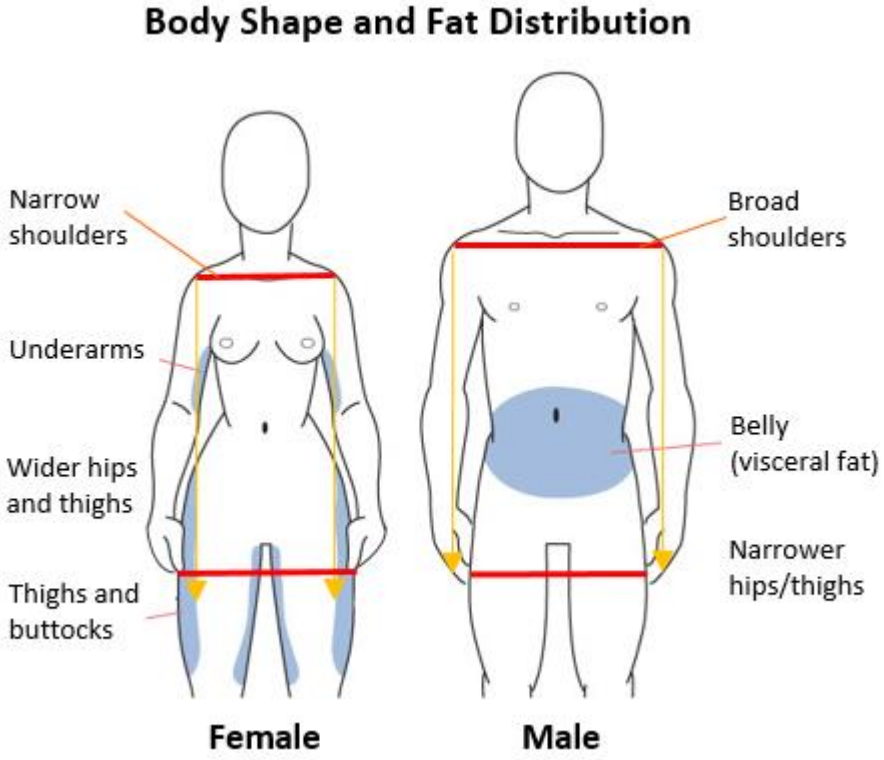


Figure 12.38 There are significant differences between the female and male body forms that are foundational and embedded within the skeletal ratios and dimensions particularly the pelvis. Seen above is the narrow shoulder to hip ratio of females, compared to the broad shoulder to hip ratio of males. These differences are integral to the female's ability to maintain pregnancy and give birth. There are also substantial differences in fat distribution, with women storing fat subcutaneously in the areas indicated, while men mostly having visceral fat storage.

The Testes

The testes (plural) and testis (singular) are enclosed in the scrotum, which is a sac sitting outside of the abdominal cavity of the body. The adequate production sperm requires a temperature that is two to three degrees F below body temperature, therefore they are stored 'outside' of the body.

Two different types of muscle (dartos of the scrotum and cremaster of the spermatic cord) help to regulate the temperature of the testes. Sperm cells are made in the seminiferous tubules of the testes.

A typical male may produce as many as **12 trillion sperm cells** in his lifetime and a typical ejaculation releases from **50 to 100 million sperm/ml**. If a man's sperm count is less than **20 million/ml**, this is considered infertile. The development of sperm takes over 70 days to mature and its maturity is overseen by a complex interaction of hormones. The histological representation of the seminiferous tubules of the testes are effectively presented below in **Fig. 12.39**.

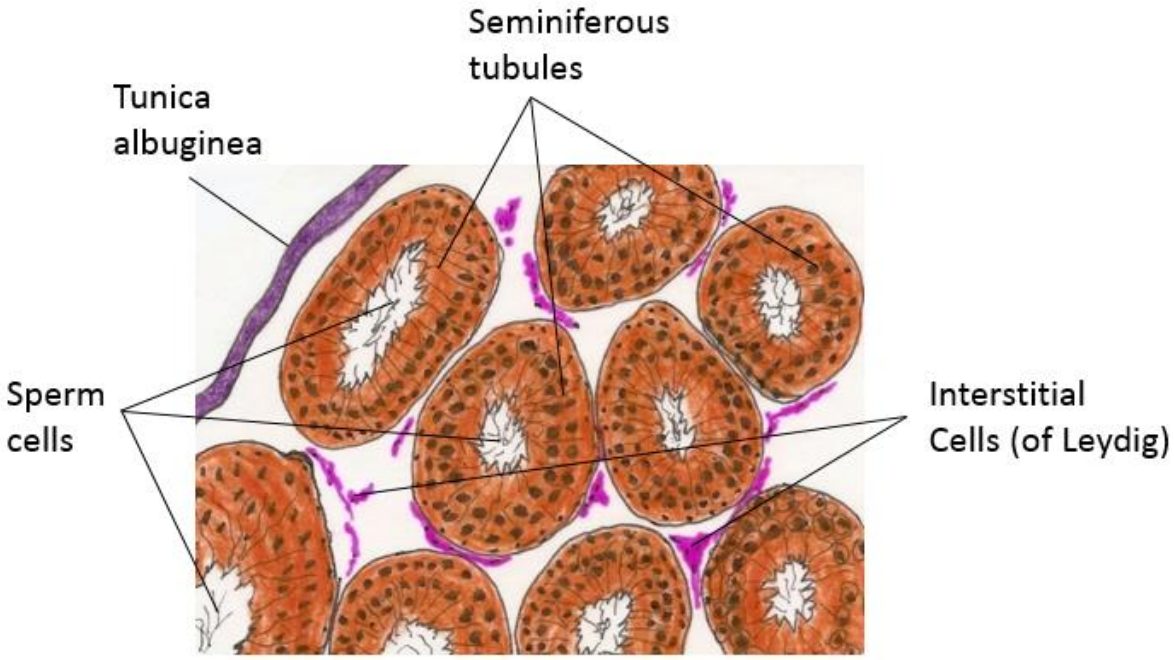


Figure 12.39 Shown are seminiferous tubules of the testes cut in cross section. The lumen of the tubules contain the developing sperm cells. The cells in between the seminiferous tubules are called interstitial cells, or the Leydig cells, or the interstitial cells of Leydig, and they are the cells of the testes that make testosterone.

Androgens are male sex hormones and the principal androgen is **testosterone**, which is secreted by the **interstitial cells** of the testes. These cells used to be called '**cells of Leydig**' so sometimes the term **interstitial cells of Leydig** is used. A small amount of testosterone is also produced by the **adrenal cortex**.

Production of testosterone begins during fetal development, continues for a short time after birth, nearly ceases during childhood, and then resumes at puberty. Testosterone is responsible for the obvious male secondary sexual characteristics such as growth and distribution of body hair, skeletal and muscular growth, and enlargement of larynx creating a low pitch voice. Testosterone is also responsible for a myriad of effects on every system of the body, including the nervous, cardiovascular and endocrine systems.

Structures of the Teste Producing Testosterone

It is the **interstitial cells** in the testes that produce testosterone. Interstitial means 'in between' and the interstitial cells, or the Leydig cells (eponym), or the interstitial cells of Leydig are the cells that are found in between the seminiferous tubules. These cells produce testosterone in the presence of **luteinizing hormone** (LH), which is also called interstitial cell stimulating hormone (ICSH) which give us a better idea of its function in male physiology.

The ICSH made and released by the anterior pituitary gland, and is the exact same molecule as luteinizing hormone, which plays a significant role in regulating the ovarian cycle and triggering the release of the ova at ovulation.

Effects of Testosterone on the Body

The most important male hormone, and arguably the most important generator of the vast difference in men and women, is **testosterone**. Men have enormous amounts of testosterone (compared to women) and this hormone is responsible for many physiological, anatomical, emotional, psychological… characteristics of men and being male.

Testosterone increases levels of growth hormone (GH) and this is why men in general are larger and have more massive structures than females. Testosterone stimulates and increases bone density and skeletal muscle hypertrophy. This is why exercising is more likely to build more bone and muscle mass in males. Though females also experience increased bone and muscle mass, **the vastly different testosterone levels makes a dramatic different between the sexes**. Testosterone also promotes bone marrow to manufacture more red blood cells, which cause males to have a higher hematocrit level than females.

Depending on the stage of life, men with very low levels of testosterone are likely to have a stature and frame that is more similar to females. Males with lower levels of testosterone are more likely to suffer from bone fractures and breaks and take longer to repair injuries that those with higher levels.

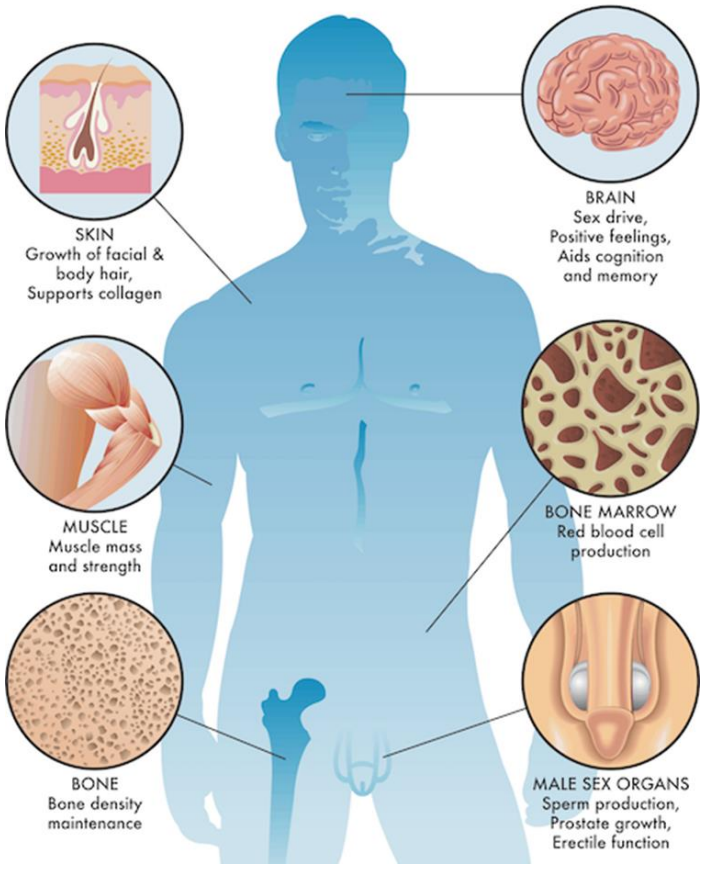


Figure 12.40 To the right shows a summary of all of the critical and significant changes that occur to a man's body due to the naturally higher levels of the sex hormone testosterone. These include greater muscle and bone mass, more regions of hair growth, increased sex drive, red blood cell production, and maintenance of the testes and sperm production.

Review Questions for Chapter 12: The Endocrine System

1. Which of the following statements is **not true** of the endocrine system?
- **a)** It is one of two major regulatory systems of the body.
- **b)** It is composed of glands that secrete chemical messengers into the blood.
- **c)** It is an important regulator of homeostatic mechanisms.
- **d)** This system regulates the sense of equilibrium and balance.
- **e)** There are interactions of this system with the nervous system

2. Which of these hormones produce effects that mimic those of the sympathetic nervous system?
- **a)** insulin
- **b)** oxytocin
- **c)** epinephrine
- **d)** growth hormone

3. Endocrine regulation
- **a)** Refers to chemical regulators that are conveyed from one organ to another via the blood stream.
- **b)** Is slower than regulation by neurotransmission.
- **c)** Differs from paracrine regulators that are secreted by the same cell on which they act, whereas endocrine regulation acts on different cell types from those that secreted them.
- **d)** a and b.
- **e)** a, b and c.

4. The endocrine gland in the peripheral body that develops from the sympathetic nervous system is the
- **a)** pancreas
- **b)** adrenal medulla
- **c)** thyroid gland
- **d)** anterior pituitary gland
- **e)** adrenal cortex

5. The hormone that aids in sodium conservation and potassium excretion is
- **a)** calcitonin
- **b)** hydrocortisone
- **c)** ADH
- **d)** aldosterone
- **e)** parathyroid hormone

6. Which hormone lowers blood glucose level?
- **a)** epinephrine
- **b)** melatonin
- **c)** insulin
- **d)** cortisol
- **e)** glucagon

7. Which hormone(s) elevate blood glucose levels?

a) epinephrine
b) glucagon
c) insulin
d) cortisol
e) a, b and d

8. If the thyroid gland is over stimulated with _____, typically a goiter will result.

a) hGH
b) TSH
c) LH
d) PRL

9. Which of the following produce testosterone?

a) adrenal medulla
b) interstitial cells of Leydig
c) adrenal cortex
d) anterior pituitary gland
e) b and c

10. Typically, a female is born with about _____ potential egg cells and only releases about _____.

a) 1 to 2 million; 400
b) 600; 400
c) 60,000; 40,000
d) 1,000; 500
e) 5,000,000; 1,000,000

Answers in Appendix B