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## Chapter 5

# The Thyroid and Parathyroid Glands

Thyroid hormones affect three fundamental physiologic processes: **cellular differentiation, growth, and metabolism**. The thyroid gland also produces another hormone called **calcitonin**, and the **parathyroid glands** secrete **parathyroid hormone**. Parathyroid hormone (parathormone) and calcitonin participate in control of calcium and phosphorus homeostasis and have significant effects on bone physiology.

### 5.1. Functional Anatomy of the Thyroid and Parathyroid Glands

The thyroid gland is located in the neck, in close approximation to the first part of the trachea. In humans, the thyroid gland has a "butterfly" shape, with two lateral lobes that are connected by a narrow section called the isthmus. Thyroid glands are brownish-red in colour.

Close examination of a thyroid gland will reveal one or more small, light-coloured nodules on or protruding from its surface - these are **parathyroid glands** (meaning "beside the thyroid").

The microscopic structure of the thyroid is quite distinctive. Thyroid epithelial cells - the cells responsible for synthesis of thyroid hormones - are arranged in spheres called **thyroid follicles**. Follicles are filled with **colloid**, a proteinaceous depot of thyroid hormone precursor. In addition to thyroid epithelial cells, the thyroid gland houses one other important endocrine cell. Nestled in spaces between thyroid follicles are *parafollicular* or **C cells**, which secrete the hormone **calcitonin**.

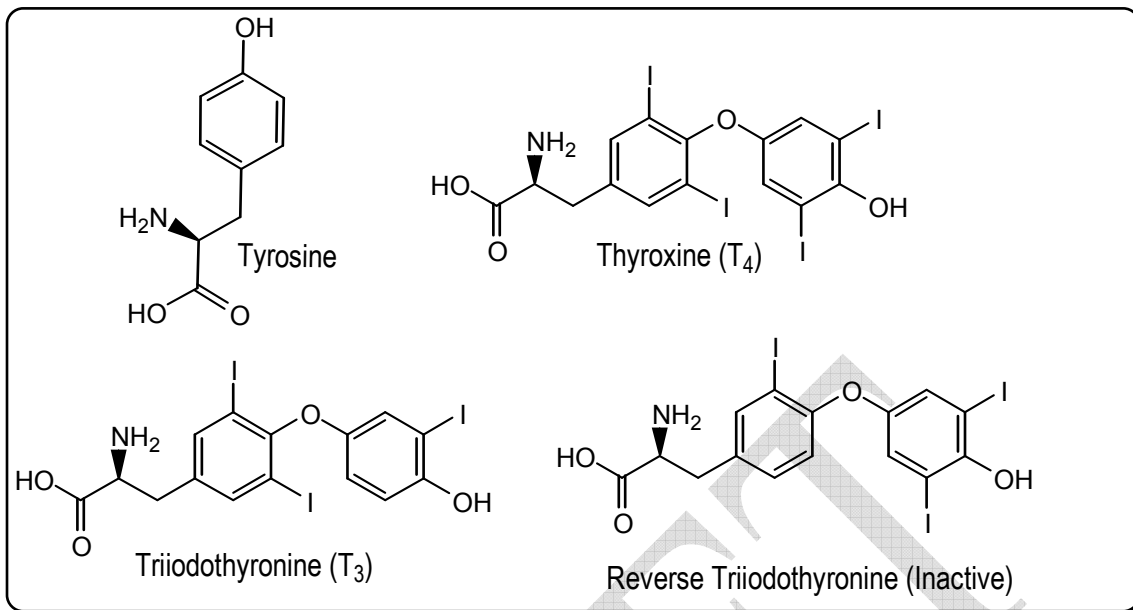
The structure of a parathyroid gland is distinctly different from a thyroid gland. The cells that synthesize and secrete parathyroid hormone are arranged in dense cords or nests around abundant capillaries.

### 5.3. Chemistry of Thyroid Hormones

Thyroid hormones are derivatives of the amino acid **tyrosine** bound covalently to **iodine**. The two principal thyroid hormones are:

- **thyroxine** (known as T4 or L-3,5,3',5'-tetraiodothyronine)
- **triiodothyronine** (T3 or L-3,5,3'-triiodothyronine).

The thyroid hormones are basically two tyrosines linked together with the addition of iodine at three or four positions on the aromatic rings. The number and position of the iodines is important. Several other iodinated molecules are generated that have little or no biological activity; so called "reverse T3" (3,3',5'-T3) is such an example.



A large majority of the thyroid hormone secreted from the thyroid gland is T<sub>4</sub>, but T<sub>3</sub> is the considerably more active hormone. Although some T<sub>3</sub> is also secreted, the bulk of the T<sub>3</sub> is derived by deiodination of T<sub>4</sub> in peripheral tissues, especially liver and kidney. Deiodination of T<sub>4</sub> also yields reverse T<sub>3</sub>, a molecule with no known metabolic activity.

Thyroid hormones are poorly soluble in water, and more than 99% of the T<sub>3</sub> and T<sub>4</sub> circulating in blood is bound to carrier proteins. The principle carrier of thyroid hormones is **thyroxine-binding globulin**, a glycoprotein synthesized in the liver. Two other carriers of import are transthyreïn and albumin. Carrier proteins allow maintenance of a stable pool of thyroid hormones from which the active, free hormones are released for uptake by target cells.

#### 5.4. Synthesis and Secretion of Thyroid Hormones

Thyroid hormones are synthesized by mechanisms fundamentally different from what is seen in other endocrine systems. Thyroid follicles serve as both factory and warehouse for production of thyroid hormones. The entire synthetic process occurs in three major steps:

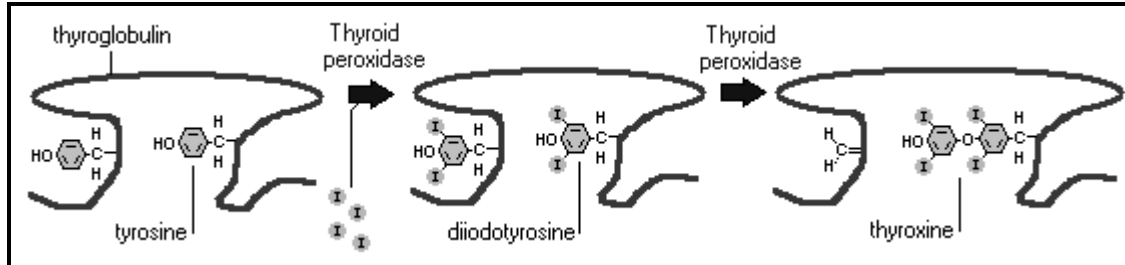
- Production and accumulation of the raw materials
- Fabrication or synthesis of the hormones on a backbone
- Release of the free hormones from the scaffold and secretion into blood

The recipe for making thyroid hormones calls for two principle raw materials:

- **Tyrosines** are provided from a large glycoprotein called **thyroglobulin**, which is synthesized by thyroid epithelial cells and secreted into the lumen of the follicle - colloid is essentially a pool of thyroglobulin. A molecule of thyroglobulin contains 134 tyrosines, although only a handful of these are actually used to synthesize T<sub>4</sub> and T<sub>3</sub>.
- **Iodine**, or more accurately iodide (I<sup>-</sup>), is taken up from blood by thyroid epithelial cells, which have on their outer plasma membrane a sodium-iodide symporter or "*iodine trap*". Once inside the cell, iodide is transported into the lumen of the follicle along with thyroglobulin.

Fabrication of thyroid hormones is conducted by the enzyme thyroid peroxidase, an integral membrane protein present in the apical (colloid-facing) plasma membrane of thyroid epithelial cells. Thyroid peroxidase catalyzes two sequential reactions:

- Iodination of tyrosines on thyroglobulin (also known as "organification of iodide").
- Synthesis of thyroxine (or triiodothyronine) from two iodotyrosines.



Through the action of thyroid peroxidase, thyroid hormones accumulate in colloid, on the surface of thyroid epithelial cells is liberate and secreted free into blood. **Thyroid hormones are excised from their thyroglobulin by digestion in lysosomes of thyroid epithelial cells.** This final act in thyroid hormone synthesis proceeds in the following steps:

- Thyroid epithelial cells ingest colloid by endocytosis from their apical borders - that colloid contains thyroglobulin decorated with thyroid hormone.
- Colloid-laden endosomes fuse with lysosomes, which contain hydrolytic enzymes that digest thyroglobulin, thereby liberating free thyroid hormones.

Finally, free thyroid hormones apparently diffuse out of lysosomes, through the basal plasma membrane of the cell, and into blood where they quickly bind to carrier proteins for transport to target cells.

### 5.5. Control of Thyroid Hormone Synthesis and Secretion

Each of the processes described above are stimulated by thyroid-stimulating hormone from the anterior pituitary gland. Binding of TSH to its receptors on thyroid epithelial cells stimulates synthesis of the iodine transporter, thyroid peroxidase and thyroglobulin. The magnitude of the TSH signal also sets the rate of endocytosis of colloid - high concentrations of TSH lead to faster rates of endocytosis, and hence, thyroid hormone release into the circulation. Conversely, when TSH levels are low, rates of thyroid hormone synthesis and release diminish.

### 5.6. Mechanism of Action and Physiologic Effects of Thyroid Hormones

#### (i) Thyroid Hormone Receptors and Mechanism of Action

Receptors for thyroid hormones are intracellular DNA-binding proteins that function as hormone-responsive transcription factors, very similar conceptually to the receptors for steroid hormones.

Despite being derived from an amino acid, thyroid hormones are hydrophobic in character and enter cells and nuclei by diffusion through cell membranes. Once inside the nucleus, the hormone binds its receptor, and the hormone-receptor complex interacts with specific sequences of DNA in the promoters of responsive genes. The effect of receptor binding to DNA is to modulate gene expression, either by stimulating or inhibiting transcription of specific genes.

#### (ii) Physiologic Effects of Thyroid Hormones

It is likely that all cells in the body are targets for thyroid hormones. While not strictly necessary for life, thyroid hormones have profound effects on many important physiologic processes, such as development, growth

and metabolism. Many of the effects of thyroid hormone have been delineated by study of deficiency and excess states, as discussed briefly below.

#### (a) Metabolism

Thyroid hormones stimulate diverse metabolic activities in most tissues, leading to an **increase in basal metabolic rate**. One consequence of this activity is to **increase body heat production**, which seems to result, at least in part, from increased oxygen consumption and rates of ATP hydrolysis. A few examples of specific metabolic effects of thyroid hormones include:

- **Lipid metabolism:** Increased thyroid hormone levels stimulate fat mobilization, leading to increased concentrations of fatty acids in plasma. They also enhance oxidation of fatty acids in many tissues. Finally, plasma concentrations of cholesterol and triglycerides are inversely correlated with thyroid hormone levels - one diagnostic indication of hypothyroidism is increased blood cholesterol concentration.
- **Carbohydrate metabolism:** Thyroid hormones stimulate almost all aspects of carbohydrate metabolism, including enhancement of insulin-dependent entry of glucose into cells and increased gluconeogenesis and glycogenolysis to generate free glucose.

#### (b) Growth

Thyroid hormones are clearly necessary for normal growth in children, as evidenced by the growth-retardation observed in thyroid deficiency. The growth-promoting effect of thyroid hormones is intimately intertwined with that of growth hormone, a clear indication that complex physiologic processes like growth depend upon multiple endocrine controls.

#### (c) Development

Normal levels of thyroid hormone are essential to the development of the foetal and neonatal brain.

#### (d) Other Effects

As mentioned above, there do not seem to be organs and tissues that are not affected by thyroid hormones. A few additional, well-documented effects of thyroid hormones include:

- **Cardiovascular system:** Thyroid hormones increases heart rate, cardiac contractility and cardiac output. They also promote vasodilation, which leads to enhanced blood flow to many organs.
- **Central nervous system:** Both decreased and increased concentrations of thyroid hormones lead to alterations in mental state. Too little thyroid hormone, and the individual tends to feel mentally sluggish, while too much induces anxiety and nervousness.
- **Reproductive system:** Normal reproductive behaviour and physiology is dependent on having essentially normal levels of thyroid hormone. Hypothyroidism in particular is commonly associated with infertility.

### 5.7. Thyroid Disease States

Disease is associated with both inadequate production and overproduction of thyroid hormones. Both types of disease are relatively common afflictions of man.

**Hypothyroidism** is the result from any condition that results in thyroid hormone deficiency. Two well-known examples include:

- **Iodine deficiency:** Iodide is absolutely necessary for production of thyroid hormones; without adequate iodine intake, thyroid hormones cannot be synthesized.
- **Primary thyroid disease:** Inflammatory diseases of the thyroid that destroy parts of the gland are clearly an important cause of hypothyroidism.

Common symptoms of hypothyroidism arising after early childhood include lethargy, fatigue, cold-intolerance, weakness, hair loss and reproductive failure. If these signs are severe, the clinical condition is called **myxedema**. In the case of iodide deficiency, the thyroid becomes inordinantly large and is called a **goiter**.

The most severe and devastating form of hypothyroidism is seen in young children with congenital thyroid deficiency. If that condition is not corrected by supplemental therapy soon after birth, the child will suffer from **cretinism**, a form of irreversible growth and mental retardation.

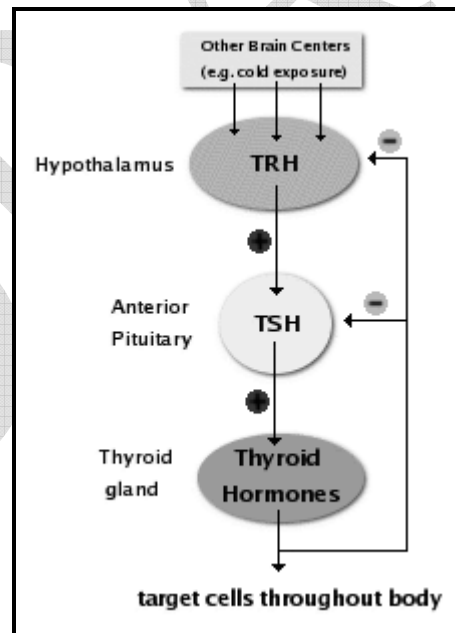
Most cases of hypothyroidism are readily treated by oral administration of synthetic thyroid hormone.

**Hyperthyroidism** results from secretion of thyroid hormones. In most species, this condition is less common than hypothyroidism. In humans the most common form of hyperthyroidism is **Graves disease**, an immune disease in which autoantibodies bind to and activate the thyroid-stimulating hormone receptor, leading to continual stimulation of thyroid hormone synthesis. Another, but rare cause of hyperthyroidism is thyrotoxicosis.

Common signs of hyperthyroidism are basically the opposite of those seen in hypothyroidism, and include nervousness, insomnia, high heart rate, eye disease and anxiety.

### 5.8. Control of Thyroid Hormone Synthesis and Secretion

The chief stimulator of thyroid hormone synthesis is thyroid-stimulating hormone from the anterior pituitary. Binding of TSH to receptors on thyroid epithelial cells seems to enhance all of the processes necessary for synthesis of thyroid hormones, including synthesis of the iodide transporter, thyroid peroxidase and thyroglobulin. The magnitude of the TSH signal also sets the rate of endocytosis of colloid - high concentrations of TSH lead to faster rates of endocytosis, and hence, thyroid hormone release into the circulation. Conversely, when TSH levels are low, rates of thyroid hormone synthesis and release diminish.



The thyroid gland is part of the hypothalamic-pituitary-thyroid axis, and control of thyroid hormone secretion is exerted by classical negative feedback, as depicted in the diagram. Thyroid-releasing hormone (TRH) from the hypothalamus stimulates TSH from the pituitary, which stimulates thyroid hormone release. As blood concentrations of thyroid hormones increase, they inhibit both TSH and TRH, leading to "shutdown" of thyroid epithelial cells. Later, when blood levels of thyroid hormone have decayed, the negative feedback signal fades, and the system wakes up again.

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A number of other factors have been shown to influence thyroid hormone secretion. In young children, exposure to a cold environment triggers TRH secretion, leading to enhanced thyroid hormone release resulting in body heat production.

## 5.9. Calcitonin

Calcitonin is a hormone known to participate in calcium and phosphorus metabolism. The major source of calcitonin is from the parafollicular or C cells in the thyroid gland, but it is also synthesized in a wide variety of other tissues, including the lung and intestinal tract. Calcitonin is a 32 amino acid peptide cleaved from a larger prohormone. It contains a single disulfide bond, which causes the amino terminus to assume the shape of a ring. Alternative splicing of the calcitonin pre-mRNA can yield a mRNA encoding calcitonin gene-related peptide; that peptide appears to function in the nervous and vascular systems. The calcitonin receptor has been cloned and shown to be a member of the seven-transmembrane, G protein-coupled receptor family.

### 5.9.1. Physiologic Effects of Calcitonin

Calcitonin plays a role in calcium and phosphorus metabolism. In particular, calcitonin has the ability to decrease blood calcium levels by effecting bone and kidney physiology:

- **Bone:** Calcitonin suppresses resorption of bone by inhibiting the activity of osteoclasts, a cell type that "digests" bone matrix, releasing calcium and phosphorus into blood.
- **Kidney:** Calcium and phosphorus are prevented from being lost in urine by reabsorption in the kidney tubules. Calcitonin inhibits tubular reabsorption of these two ions, leading to increased rates of their loss in urine.

### 5.9.2. Control of Calcitonin Secretion

**The most prominent factor controlling calcitonin secretion is the extracellular concentration of ionized calcium.** Elevated blood calcium levels strongly stimulate calcitonin secretion, and secretion is suppressed when calcium concentration falls below normal.

### 5.9.2. Disease States

A large number of diseases are associated with abnormally increased or decreased levels of calcitonin, but pathologic effects of abnormal calcitonin secretion *per se* are not generally recognized.

There are several therapeutic uses for calcitonin. It is used to treat hypercalcemia resulting from a number of causes, and has been a valuable therapy for Paget disease, which is a disorder in bone remodeling. Calcitonin also appears to be a valuable aid in the management of certain types of osteoporosis.

## 5.10. Endocrine Control of Calcium and Phosphate Homeostasis

### 5.10.1. Body Distribution of Calcium and Phosphate

There are three major pools of calcium in the body:

- **Intracellular calcium:** A large majority of calcium within cells is sequestered in mitochondria and endoplasmic reticulum. Intracellular free calcium concentrations fluctuate greatly, from roughly 100 nM to greater than 1  $\mu$ M, due to release from cellular stores or influx from extracellular fluid. These fluctuations are integral to calcium's role in intracellular signaling, enzyme activation and muscle contractions.
- **Calcium in blood and extracellular fluid:** Roughly half of the calcium in blood is bound to proteins. The concentration of ionized calcium in this compartment is normally almost invariant at approximately 1 mM, or 10,000 times the basal concentration of free calcium within cells. Also, the concentration of phosphorus in blood is essentially identical to that of calcium.
- **Bone calcium:** A vast majority of body calcium is in bone. Within bone, 99% of the calcium is tied up in the mineral phase, but the remaining 1% is in a pool that can rapidly exchange with extracellular calcium.

As with calcium, the majority of body phosphate (approximately 85%) is present in the mineral phase of bone. The remainder of body phosphate is present in a variety of inorganic and organic compounds distributed within both intracellular and extracellular compartments. Normal blood concentrations of phosphate are very similar to calcium.

### 5.10.2. Fluxes of Calcium and Phosphate

Maintaining constant concentrations of calcium in blood requires frequent adjustments, which can be described as fluxes of calcium between blood and other body compartments. Three organs participate in supplying calcium to blood and removing it from blood when necessary:

- The **small intestine** is the site where dietary calcium is absorbed. Importantly, efficient absorption of calcium in the small intestine is dependent on expression of a calcium-binding protein in epithelial cells.
- **Bone** serves as a vast reservoir of calcium. Stimulating net resorption of bone mineral releases calcium and phosphate into blood, and suppressing this effect allows calcium to be deposited in bone.
- The **kidney** is critically important in calcium homeostasis. Under normal blood calcium concentrations, almost all of the calcium that enters glomerular filtrate is reabsorbed from the tubular system back into blood, which preserves blood calcium levels. If tubular reabsorption of calcium decreases, calcium is lost by excretion into urine.

### 5.11. Control Systems

Maintaining normal blood calcium and phosphorus concentrations is managed through the concerted action of three hormones that control fluxes of calcium in and out of blood and extracellular fluid:

Parathyroid hormone serves to increase blood concentrations of calcium. Parathyroid hormone preserves blood calcium by several major effects:

- Stimulates production of the biologically-active form of vitamin D within the kidney.
- Facilitates mobilization of calcium and phosphate from bone. To prevent detrimental increases in phosphate, parathyroid hormone also has a potent effect on the kidney to eliminate phosphate (phosphaturic effect).
- Maximizes tubular reabsorption of calcium within the kidney. This activity results in minimal losses of calcium in urine.

Vitamin D acts also to increase blood concentrations of calcium. It is generated through the activity of parathyroid hormone within the kidney. The most important effect of vitamin D is to facilitate absorption of calcium from the small intestine. In concert with parathyroid hormone, vitamin D also enhances fluxes of calcium out of bone.

Calcitonin is a hormone that functions to reduce blood calcium levels. It is secreted in response to hypercalcemia and has at least two effects:

- Suppression of renal tubular reabsorption of calcium. i.e., calcitonin enhances excretion of calcium into urine.
- Inhibition of bone resorption, which would minimize fluxes of calcium from bone into blood.
- Although calcitonin has significant calcium-lowering effects in some species, it appears to have a minimal influence on blood calcium levels in humans.

### 5.12. ParaThyroid Hormone

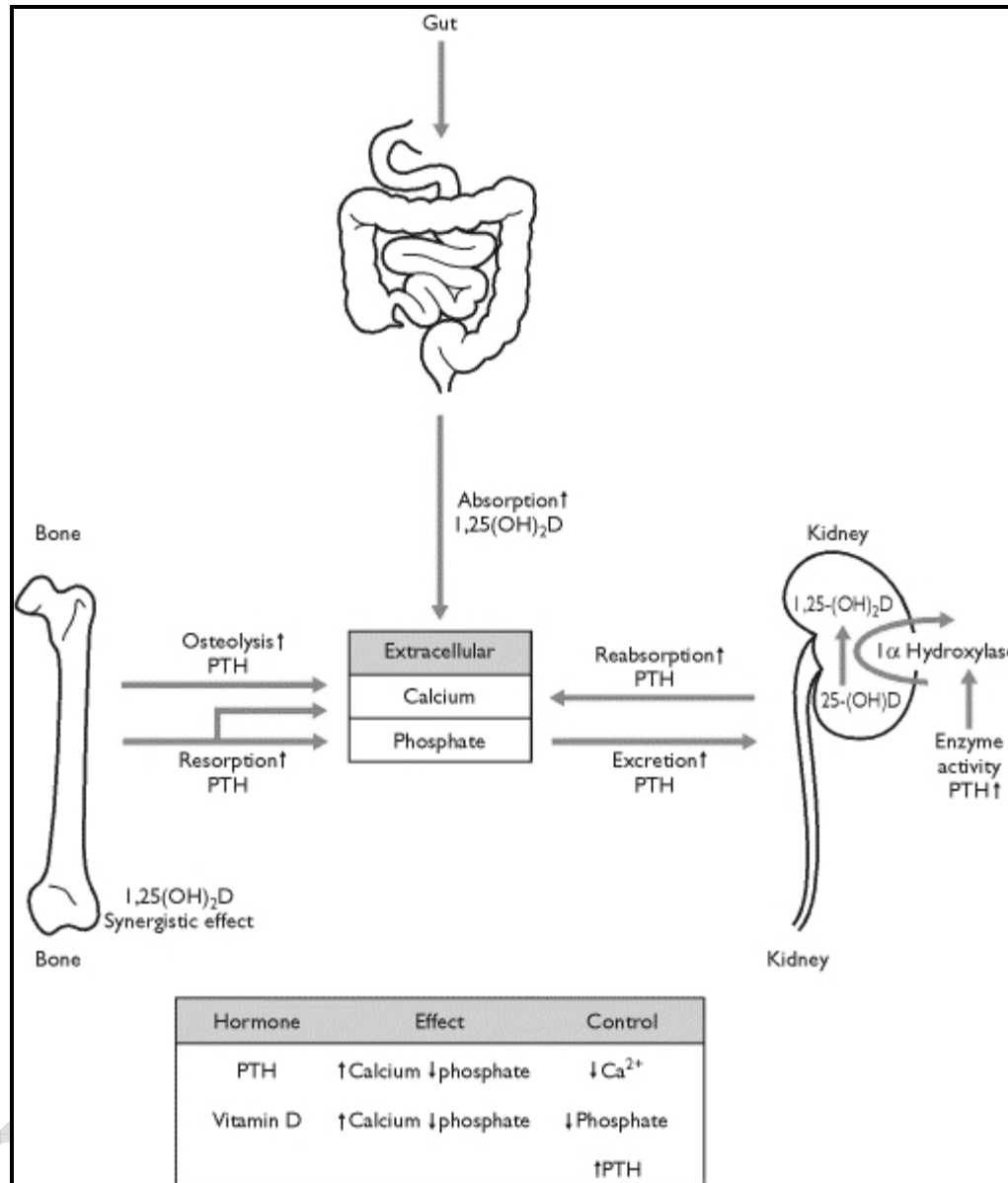
Parathyroid hormone is the most important endocrine regulator of calcium and phosphorus concentration in extracellular fluid. This hormone is secreted from cells of the parathyroid glands and finds its major target cells in bone and kidney. Another hormone, parathyroid hormone-related protein, binds to the same receptor

as parathyroid hormone and has major effects on development. Like most other protein hormones, parathyroid hormone is synthesized as a prehormone. After intracellular processing, the mature hormone is packaged within the Golgi into secretory vesicles, the secreted into blood by exocytosis. Parathyroid hormone is secreted as a linear protein of 84 amino acids.

### 5.12.1. Physiologic Effects of Parathyroid Hormone

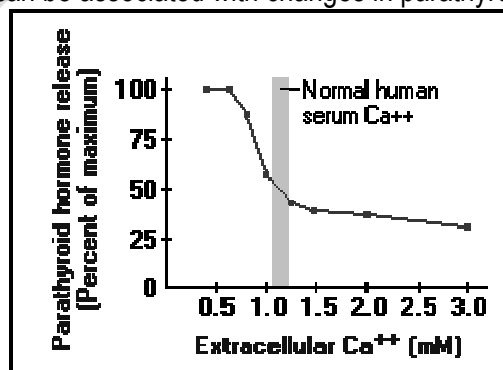
Writing a job description for parathyroid hormone is straightforward: if calcium ion concentrations in extracellular fluid fall below normal, bring them back within the normal range. In conjunction with increasing calcium concentration, the concentration of phosphate ion in blood is reduced. Parathyroid hormone accomplishes its job by stimulating at least three processes:

- **Mobilization of calcium from bone:** Parathyroid stimulates osteoclasts to reabsorb bone mineral, liberating calcium into blood.
- **Enhancing absorption of calcium from the small intestine:** Facilitating calcium absorption from the small intestine would clearly serve to elevate blood levels of calcium. Parathyroid hormone stimulates this process, but *indirectly* by stimulating production of the active form of vitamin D in the kidney. Vitamin D induces synthesis of a calcium-binding protein in intestinal epithelial cells that facilitates efficient absorption of calcium into blood.
- **Suppression of calcium loss in urine:** In addition to stimulating fluxes of calcium into blood from bone and intestine, parathyroid hormone puts a brake on excretion of calcium in urine, thus conserving calcium in blood. This effect is mediated by stimulating tubular reabsorption of calcium. Another effect of parathyroid hormone on the kidney is to stimulate loss of phosphate ions in urine.



### 5.12.2. Control of Parathyroid Hormone Secretion

Parathyroid hormone is released in response to low extracellular concentrations of free calcium. Changes in blood phosphate concentration can be associated with changes in parathyroid hormone secretion.



When calcium concentrations fall below the normal range, there is a steep increase in secretion of parathyroid hormone. Low levels of the hormone are secreted even when blood calcium levels are high. The parathyroid cell monitors extracellular free calcium concentration via an integral membrane protein that functions as a calcium-sensing receptor.

### 5.12.3. Disease States

Both increased and decreased secretion of parathyroid hormone are recognized as causes of serious disease in man. Excessive secretion of parathyroid hormone is seen in two forms:

- **Primary hyperparathyroidism** is the result of parathyroid gland disease, most commonly due to a parathyroid tumour (adenoma) which secretes the hormone without proper regulation. Common manifestations of this disorder are chronic elevations of blood calcium concentration (hypercalcemia), kidney stones and decalcification of bone.
- **Secondary hyperparathyroidism** is the situation where disease outside of the parathyroid gland leads to excessive secretion of parathyroid hormone. A common cause of this disorder is kidney disease - if the kidneys are unable to reabsorb calcium, blood calcium levels will fall, stimulating continual secretion of parathyroid hormone to maintain normal calcium levels in blood. Secondary hyperparathyroidism can also result from inadequate nutrition – e.g., diets that are deficient in calcium or vitamin D, or which contain excessive phosphorus (e.g. all meat diets for carnivores).

A prominent effect of secondary hyperparathyroidism is decalcification of bone, leading to pathologic fractures or "rubber bones".

Chronic secretion or continuous infusion of parathyroid hormone leads to decalcification of bone and loss of bone mass. However, in certain situations, treatment with parathyroid hormone can actually stimulate an increase in bone mass and bone strength. This seemingly paradoxical effect occurs when the hormone is administered in pulses (e.g. by once daily injection), and such treatment appears to be an effective therapy for diseases such as osteoporosis.

Inadequate production of parathyroid hormone - **hypoparathyroidism** - typically results in decreased concentrations of calcium and increased concentrations of phosphorus in blood. Common causes of this disorder include surgical removal of the parathyroid glands and disease processes that lead to destruction of parathyroid glands. The resulting hypocalcemia often leads to tetany and convulsions, and can be acutely life-threatening. Treatment focuses on restoring normal blood calcium concentrations by calcium infusions, oral calcium supplements and vitamin D therapy.