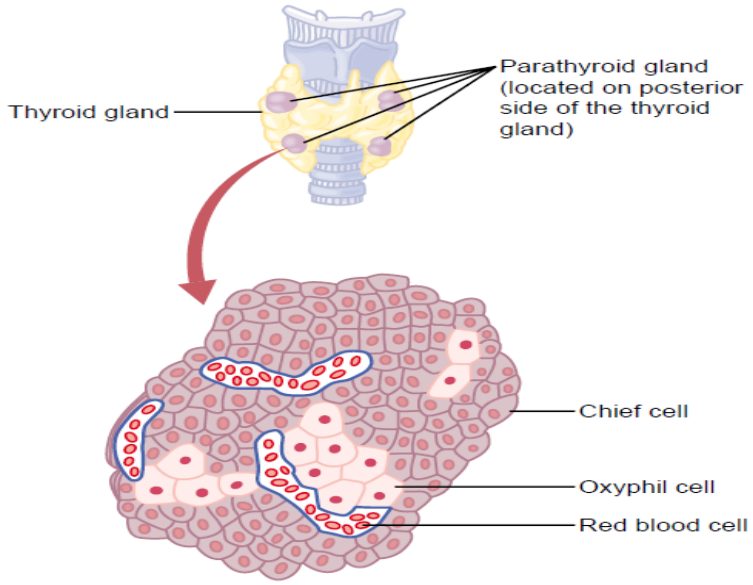
Lecture No.7



Parathyroid Hormone

Parathyroid hormone provides a powerful mechanism for controlling extracellular calcium and phosphate concentrations by regulating intestinal reabsorption,renal excretion, and exchange between the extracellular fluid and bone of these ions. Excess activity of the parathyroid gland causes rapid absorption of calcium salts from the bones, with resultant *hypercalcemia* in the extracellular fluid; conversely, hypofunction of the parathyroid glands causes *hypocalcemia*, often with resultant tetany.

***Physiologic Anatomy of the Parathyroid Glands*.**

Normally there are four parathyroid glands in humans; they are located immediately behind the thyroid gland—one behind each of the upper and each of the lower poles of the thyroid. Each parathyroid gland is about 6 millimeters long, 3 millimeters wide, and 2 millimeters thick and has a macroscopic appearance of dark brown fat. The parathyroid glands are difficult to locate during thyroid operations because they often look like just another lobule of the thyroid gland. For this reason, before the importance of these glands was generally recognized, total or subtotal thyroidectomy frequently resulted in removal of the parathyroid glands as well. Removal of half the parathyroid glands usually causes no major physiologic abnormalities. However, removal of three of the four normal glands causes transient hypoparathyroidism. But even a small quantity of remaining parathyroid tissue is usually capable of hypertrophying satisfactorily to perform the function of all the glands. The parathyroid gland of the adult human being, shown in above figure contains mainly

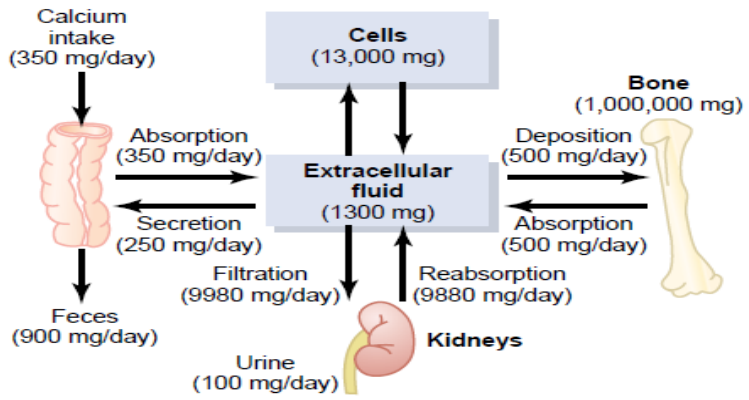
chief cells and a small to moderate number of ***oxyphil cells***, but oxyphil cells are absent in many animals and in young humans. The chief cells are believed to secrete most, if not all, of the PTH. The function of the oxyphil cells is not certain, but they are believed to be modified or depleted chief cells that no longer secrete hormone.

Effect of Parathyroid Hormone on Calcium and Phosphate Concentrations in the Extracellular Fluid

The figure below shows the approximate effects on the blood calcium and phosphate concentrations caused by suddenly infusing PTH into an animal and continuing this for several hours. Note that at the onset of infusion the calcium ion concentration begins to rise and reaches a plateau in about 4 hours.The phosphate concentration, however, falls more rapidly than the calcium rises and reaches a depressed level within 1 or 2 hours. The rise in calcium concentration is caused principally by two effects: (1) an effect of PTH to increase calcium and phosphate absorption from the bone and (2) a rapid effect of PTH to decrease the excretion of calcium by the kidneys. The decline in phosphate concentration is caused by a strong effect of PTH to increase renal phosphate excretion, an effect that is usually great enough to override increased phosphate absorption from the bone.

Parathyroid Hormone Increases Calcium and Phosphate Absorption from the Bone

PTH has two effects on bone in causing absorption of calcium and phosphate. One is a rapid phase that begins in minutes and increases progressively for several hours. This phase results from activation of the already existing bone cells (mainly the osteocytes) to promote calcium and phosphate absorption. The second phase is a much slower one, requiring several days or even weeks to become fully developed; it results from proliferation of the osteoclasts, followed by greatly increased osteoclastic reabsorption of the bone itself, not merely absorption of the calcium phosphate salts from the bone.



Rapid Phase of Calcium and Phosphate Absorption—Osteolysis.

When large quantities of PTH are injected, the calcium ion concentration in the blood begins to rise within minutes, long before any new bone cells can be developed. Histological and physiologic studies have shown that PTH causes removal of bone salts from two areas in the bone: (1) from the bone matrix in the vicinity of the osteocytes lying within the bone itself and (2) in the vicinity of the osteoblasts along the bone surface.

But where does PTH fit into this picture?

First, the cell membranes of both the osteoblasts and the osteocytes have receptor proteins for binding PTH.

PTH can activate the calcium pump strongly, thereby causing rapid removal of calcium phosphate salts from those amorphous bone crystals that lie near the cells. PTH is believed to stimulate this pump by increasing the calcium permeability of the bone fluid side of the osteocytic membrane, thus allowing calcium ions to diffuse into the membrane cells from the bone fluid. Then the calcium pump on the other side of the cell membrane transfers the calcium ions the rest of the way into the extracellular fluid.

***Slow Phase of Bone Absorption and Calcium Phosphate Release—Activation of the Osteoclasts*.**

A much better known effect of PTH and one for which the evidence is much clearer is its activation of the osteoclasts. Yet the osteoclasts do not themselves have membrane receptor proteins for PTH. Instead, it is believed that the activated osteoblasts and osteocytes send a secondary but unknown "signal" to the osteoclasts, causing them to set about their usual task of gobbling up the bone over a period of weeks or months.

Activation of the osteoclastic system occurs in two stages: (1) immediate activation of the osteoclasts that are already formed and (2) formation of new osteoclasts. Several days of excess PTH usually cause the osteoclastic system to become well developed, but it can continue to grow for months under the influence of strong PTH stimulation.

Parathyroid Hormone Decreases Calcium Excretion and Increases Phosphate Excretion by the Kidneys

Administration of PTH causes rapid loss of phosphate in the urine owing to the effect of the hormone to diminish proximal tubular reabsorption of phosphate ions. PTH also increases renal tubular reabsorption of calcium at the same time that it diminishes phosphate reabsorption. Moreover, it increases the rate of reabsorption of magnesium ions and hydrogen ions while it decreases the reabsorption of sodium, potassium, and amino acid ions in much the same way that it affects phosphate. The increased calcium absorption occurs mainly in the *late distal tubules*, the *collecting*

tubules, the early collecting ducts, and possibly the ascending loop of Henle to a lesser extent. Were it not for the effect of PTH on the kidneys to increase calcium reabsorption, continual loss of calcium into the urine would eventually deplete both the extracellular fluid and the bones of this mineral.

Parathyroid Hormone Increases Intestinal Absorption of Calcium and Phosphate

At this point, we should be reminded again that PTH greatly enhances both calcium and phosphate absorption from the intestines by increasing the formation in the kidneys of 1,25-dihydroxycholecalciferol from vitamin D.

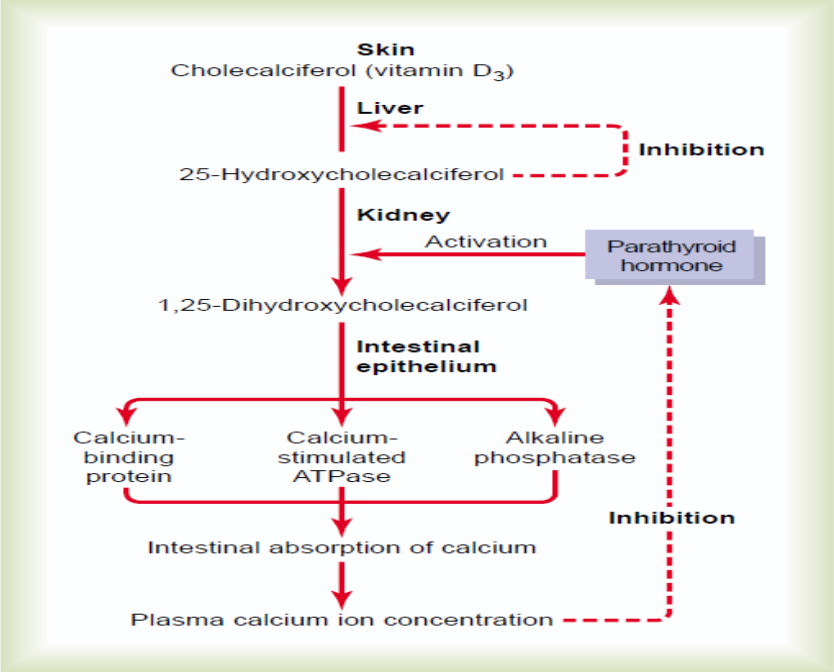
Cyclic Adenosine Monophosphate Mediates the Effects of Parathyroid Hormone.

A large share of the effect of PTH on its target organs is mediated by the cyclic adenosine monophosphate (cAMP) *second messenger* mechanism. Within a few minutes after PTH administration, the concentration of cAMP increases in theosteocytes, osteoclasts, and other target cells. This cAMP in turn is probably responsible for such functions as osteoclastic secretion of enzymes and acids to cause bone reabsorption and formation of 1,25- dihydroxycholecalciferol in the kidneys. There areprobably other direct effects of PTH that function independently of the second messenger mechanism.

Formation of 1,25-Dihydroxycholecalciferol in the Kidneys and Its Control by Parathyroid Hormone.

The figure below also shows the conversion in the proximal tubules of the kidneys of 25-hydroxycholecalciferol to *1,25dihydroxycholecalciferol*.

This latter substance is by far the most active form of vitamin D, because the previous products in the scheme of the figure have less than 1/1000 of the vitamin D effect. Therefore, in the absence of the kidneys, vitamin D loses almost all its effectiveness. Note also in this figure that the conversion of 25-hydroxycholecalciferol to 1,25dihydroxycholecalciferol requires PTH. In the absence of PTH, almost none of the 1,25-dihydroxycholecalciferol is formed. Therefore, PTH exerts a potent influence in determining the functional effects of vitamin D in the body.



"Hormonal" Effect of Vitamin D to Promote Intestinal Calcium Absorption.

1,25-Dihydroxycholecalciferol itself functions as a type of "hormone" to promote intestinal absorption of calcium. It does this principally by increasing, over a period of about 2 days, formation of a *calcium-binding protein* in the intestinal epithelial cells. This protein functions in the brush border of these cells to transport calcium into the cell cytoplasm, and the calcium then moves through the basolateral membrane of the cell by facilitated diffusion.The rate of calcium absorption is directly proportional to the quantity of this calcium-binding protein. Furthermore, this protein remains in the cells for several weeks after the 1,25-dihydroxycholecalciferol has been removed from the body, thus causing a prolonged effect on calcium absorption. Other effects of 1,25-dihydroxycholecalciferol that might play a role in promoting calcium absorption are the formation of (1) a calcium-stimulated ATPase in the brush border of the epithelial cells and (2) an alkaline phosphatase in the epithelial cells. The precise details of all these effects are unclear.

Control of Parathyroid Secretion by Calcium Ion Concentration

Even the slightest decrease in calcium ion concentration in the extracellular fluid causes the parathyroid glands to increase their rate of secretion within minutes; if the decreased calcium concentration persists, the glands will hypertrophy, sometimes fivefold or more. For instance, the parathyroid glands become greatly enlarged in *rickets*, in which the level of calcium is usually depressed only a small amount; also, they become greatly enlarged in *pregnancy*, even though the decrease in calcium ion concentration in the mother's extracellular fluid is hardly

measurable; and they are greatly enlarged during *lactation* because calcium is used for milk formation. Conversely, conditions that increase the calcium ion concentration above normal cause decreased activity and reduced size of the parathyroid glands. Such conditions include (1) excess quantities of calcium in the diet, (2) increased vitamin D in the diet, and (3) bone absorption caused by factors other than PTH (for example, bone absorption caused by disuse of the bones).

Calcitonin

Calcitonin, a peptide hormone secreted by the thyroid gland, tends to *decrease* plasma calcium concentration and, in general, has effects opposite to those of PTH. However, the quantitative role of calcitonin is far less than that of PTH in regulating calcium ion concentration. Synthesis and secretion of calcitonin occur in the *parafollicular cells*, or *C cells*, lying in the interstitial fluid between the follicles of the thyroid gland. These cells constitute only about 0.1 per cent of the human thyroid gland and are the remnants of the *ultimobrachial glands* of lower animals such as fish, amphibians, reptiles, and birds. Calcitonin is a 32-amino acid peptide with a molecular weight of about 3400.

Increased Plasma Calcium Concentration Stimulates Calcitonin Secretion.

The primary stimulus for calcitonin secretion is increased plasma calcium ion concentration. This contrasts with PTH secretion, which is stimulated by decreased calcium concentration. In young animals, but much less so in older animals and in humans, an increase in plasma calcium concentration of about 10 per cent causes an immediate twofold or more increase in the rate of secretion of calcitonin . This provides a second hormonal feedback mechanism for controlling the plasma calcium ion concentration, but one that is relatively weak and works in a way opposite that of the PTH system.

Calcitonin Decreases Plasma Calcium Concentration.

In some young animals, calcitonin decreases blood calcium ion concentration rapidly, beginning within minutes after injection of the calcitonin, in at least two ways.

1. The immediate effect is to decrease the absorptive activities of the osteoclasts and possibly the osteolytic effect of the osteocytic membrane throughout the bone, thus shifting the balance in favor of deposition of calcium in the exchangeable bone calcium salts. This effect is especially significant in young animals because of the rapid interchange of absorbed and deposited calcium.
2. The second and more prolonged effect of calcitonin is to decrease the formation of new osteoclasts.Also, because osteoclastic resorption of bone leads secondarily to osteoblastic activity, decreased numbers of

osteoclasts are followed by decreased numbers of osteoblasts. Therefore, over a long period, the net result is reduced osteoclastic and osteoblastic activity and, consequently, very little prolonged effect on plasma calcium ion concentration. That is, the effect on plasma calcium is mainly a transient one, lasting for a few hours to a few days at most. Calcitonin also has minor effects on calcium handling in the kidney tubules and the intestines. Again, the effects are opposite those of PTH, but they appear to be of such little import that they are seldom considered.

Calcitonin Has a Weak Effect on Plasma Calcium Concentration in the Adult Human.

The reason for the weak effect of calcitonin on plasma calcium is twofold. First, any initial reduction of the calcium ion concentration caused by calcitonin leads within hours to a powerful stimulation of PTH secretion, which almost overrides the calcitonin effect. When the thyroid gland is removed and calcitonin is no longer secreted, the longterm blood calcium ion concentration is not measurably altered, which again demonstrates the overriding effect of the PTH system of control.

Second, in the adult, the daily rates of absorption and deposition of calcium are small, and even after the rate of absorption is slowed by calcitonin, this still has only a small effect on plasma calcium ion concentration. The effect of calcitonin in children is much greater because bone remodeling occurs rapidly in children, with absorption and deposition of calcium as great as 5 grams or more per day—equal to 5 to 10 times the total calcium in all the extracellular fluid. Also, in certain bone diseases, such as *Paget's disease*, in which osteoclastic activity is greatly accelerated, calcitonin has a much more potent effect of reducing the calcium absorption.

Hypoparathyroidism

When the parathyroid glands do not secrete sufficient PTH, the osteocytic reabsorption of exchangeable calcium decreases and the osteoclasts become almost totally inactive. As a result, calcium reabsorption from the bones is so depressed that the level of calcium in the body fluids decreases. Yet, because calcium and phosphates are not being absorbed from the bone, the bone usually remains strong. When the parathyroid glands are suddenly removed, the calcium level in the blood falls from the normal of 9.4 mg/dl to 6 to 7 mg/dl within 2 to 3 days, and the blood phosphate concentration may double.When this low calcium level is reached, the usual signs of tetany develop. Among the muscles of the body especially sensitive to tetanic spasm are the laryngeal muscles. Spasm of these muscles obstructs respiration, which is the usual cause of death in tetany unless appropriate treatment is applied.