Lecture #: 5

Endocrine system

Subject: Calcium Homeostasis, Parathyroid Functions.
Doctor: Salim Khresha #5
Done By: Slides
Date: 20/3/2013

[Physiology]
Parathyroids

1) Four small glands composed of cords of cells which secrete Parathyroid hormone - PARATHORMONE or PTH.

2) Situated behind thyroid.

3) Each weighs from 20-50 mg in adult.

4) PARATHORMONE acts on kidney tubules, bone, and on gut to maintain ionized blood calcium level at 11 mg/100 ml plasma (necessary for normal neuromuscular excitability).

5) Function of eosinophil cells is unknown.

6) General circulation to all tissues of the body.

But not all tissues are sensitive to it.

It plays an important role in calcium and phosphate metabolism.
Figure 79-10 The four parathyroid glands lie immediately behind the thyroid gland. Almost all of the parathyroid hormone (PTH) is synthesized and secreted by the chief cells. The function of the oxyphil cells is uncertain, but they may be modified or depleted chief cells that no longer secrete PTH.
1. The parathyroid glands develop at 5-14 weeks of gestation.
2. PTH is a single chain protein (9600 molecular weight) that contains 84 amino acids.
   The biologic activity of the hormone resides within a.a.1-34.
3. PTH interacts with receptors on the surface of the target cells increasing the formation of cAMP, IP & diacylglycerol.
4. PTH is free in plasma with half life 25 m.
5. PTH is essential for life, without it Ca++ falls in plasma neuromuscular excitability ↑, tetany & death occurs.
6. The dominant regulator of PTH secretion is the plasma Ca++ level.
7. Ca++ also regulates the size & the number of parathyroid cells.
8. Hypomagnesemia stimulates PTH secretion such as Ca++ but less potent.
10. 1,25 (OH)₂ -D directly reduces PTH secretion.
FIGURE 36.7 Effects of parathyroid hormone (PTH) on calcium and phosphate metabolism.
FIGURE 39-7 Overview of parathyroid hormone (PTH) actions. PTH acts directly on bone and kidney to increase calcium influx into plasma. By stimulating 1,25-(OH)₂-D synthesis, PTH indirectly also increases calcium absorption from the gut. Thus plasma calcium level increases. In contrast, PTH inhibits renal tubular resorption of phosphate, thereby increasing urinary phosphate excretion. This effect quantitatively offsets entry of phosphate from bone and gut. Therefore plasma phosphate level decreases.
UNDERACTIVITY of PARATHYROIDs

Atrophy or removal of Parathyroid tissue causes a fall in BLOOD CALCIUM level and increased excitability of Neuromuscular tissue. This leads to severe convulsive disorder - TETANY.

Usual Manifestations:-
- TWITCHINGS,
- NERVOSNESS,
- OCCASIONAL SPASMS
- OF FACIAL AND LIMB MUSCLES.

PARATHYROID GLANDS

Inadequate Production of PTH

BONE

Reduced mobilization of Ca and P

Increased amounts of Ca and P in bones

KIDNEY

Diminished tubular reabsorption of Ca

Decreased phosphate excretion

Increase in urinary Ca

GUT

Diminished absorption of dietary Ca

Fall in Concentration of ionized Calcium

[Rise in plasma phosphate]

If concentration of Ca in blood falls below 6mg/100ml plasma.

[Note the inverse relationship between plasma calcium and inorganic phosphate]

Symptoms are relieved by injection of Calcium, large doses of a Vit.D compound and Parathormone.
OVERACTIVITY of PARATHYROIDs

Overactivity of the Parathyroids (due often to tumour) leads to rise in BLOOD CALCIUM level and eventually to OSTEITIS FIBROSA CYSTICA.

**PARATHYROID GLANDS**

Overproduction of PTH

- **BONE**
  - Greatly increased mobilization of Ca and P
  - Events amount of Ca and P in Bone

- **KIDNEY**
  - Greatly increased tubular reabsorption of Ca and tubular secretion of P
  - Great loss of P in Urine
  - Great increase in Concentration of Ca in Blood
    - Plasma Ca may be over 10mg/100ml → Increased Viscosity of Plasma,
    - Deposition of Calcium in Unusual Sites, e.g., Kidney
    - Signs of Toxicity → Kidney
      - Nausea, vomiting, loss of appetite, etc.

- **GUT**
  - Great increase in absorption of dietary Ca

**OSTEITIS FIBROSA CYSTICA**

- Eventual Softening and deformity of bones

The increased level of blood calcium eventually leads to excessive loss of CALCIUM in URINE (in spite of reabsorption) and also of WATER since the salt is excreted in solution. POLYURIA and THIRST result.

*Excision of the overactive Parathyroid tissue abolishes syndrome.*
Figure 79-5 Bone resorption by osteoclasts. Parathyroid hormone (PTH) binds to receptors on osteoblasts, causing them to release osteoprotegerin ligand (OPGL), which binds to receptors on preosteoclast cells. This causes the cells to differentiate into mature osteoclasts. The osteoclasts then develop a ruffled border and release enzymes from lysosomes, as well as acids that promote bone resorption. Osteocytes are osteoblasts that have become encased in bone matrix during bone tissue production; the osteocytes form a system of interconnected cells that spread all through the bone.
Vitamin D

Vitamin D, in conjunction with PTH, is the second major regulatory hormone for Ca\(^2^+\) and phosphate metabolism. The roles of PTH and vitamin D can be distinguished as follows. The role of PTH is to maintain the plasma Ca\(^2^+\) concentration, and its actions are coordinated to increase the ionized Ca\(^2^+\) concentration toward normal. The role of vitamin D is to promote mineralization of new bone, and its actions are coordinated to increase both Ca\(^2^+\) and phosphate concentrations in plasma so that these elements can be deposited in new bone mineral.

Bone. In bone, 1,25-dihydroxycholecalciferol acts synergistically with PTH to stimulate osteoclast activity and bone resorption. This action may seem paradoxical, since the overall action of 1,25-dihydroxycholecalciferol is to promote bone mineralization. However, mineralized "old" bone is resorbed to provide more Ca\(^2^+\) and phosphate to ECF so that "new" bone can be mineralized (bone remodeling).
Vitamin D & its Metabolism

1. Vitamin D, is a major regulator of calcium & phosphate metabolism.

2. Vitamin D is a hormone in the sense that it is synthesized in the body, although not by an endocrine gland; after further processing, it is transported via the circulation to act on target cells.

3. It is a vitamin in the sense that when it cannot be synthesized in sufficient quantities, it must be ingested in minimal amounts for health to be maintained.


5. The sterol structure of the synthesized form of vitamin D (D₃) differs slightly from the form usually ingested (D₂).

6. Vitamins D₃ & D₂ are essentially prohormones that undergo identical processing that converts them to molecules with identical qualitative & quantitative actions.

7. Once vitamin D enters the circulation from the skin or the gut, it is concentrated in the liver. There it is hydroxylated to 25-OH-D. This molecule is transported to the kidney where it undergoes alternative fates.

8. 24,25-(OH)₂-D is only 1/20th as potent as 1,25-(OH)₂-D & mainly serves to dispose of excess vitamin D.

9. Vitamin D, 25-OH-D & 1,25-(OH)₂-D circulate bound to a protein carrier. 1,25-(OH)₂-D has by far the lowest concentration & the shortest half-life of the three.
\[ \downarrow \text{Plasma calcium} \]

\[ \downarrow \text{Plasma PTH} \]

\[ \uparrow \text{Renal } 1\alpha\text{-hydroxylase activity} \]

\[ \uparrow 1,25-(\text{OH})_2 \text{D}_3 \text{ formation} \]

\[ \uparrow \text{Plasma } 1,25-(\text{OH})_2 \text{D}_3 \]

- **Kidneys**
  - \[ \uparrow \text{Phosphate reabsorption} \]
  - \[ \uparrow \text{Calcium reabsorption} \]

- **Intestine**
  - \[ \uparrow \text{Phosphate absorption} \]
  - \[ \uparrow \text{Calcium absorption} \]

- **Bone**
  - promotes PTH action

\[ \downarrow \text{Urinary excretion of phosphate} \]

\[ \downarrow \text{Urinary excretion of calcium} \]

\[ \uparrow \text{Plasma phosphate} \]

\[ \uparrow \text{Plasma calcium} \]

**FIGURE 36.9** Effects of 1,25-dihydroxycholecalciferol [1,25-(OH)_2 D_3] on calcium and phosphate metabolism.
FIGURE 3B-8  Vitamin D metabolism. Whether synthesized in the skin or absorbed from the diet, vitamin D undergoes 25-hydroxylation in the liver. In the kidney, it is further hydroxylated in the 1 position when more biological activity is required or in the 24 position when less biological activity is required.
### TABLE 51-2. Vitamin D metabolism in humans

<table>
<thead>
<tr>
<th>Vitamin D compound</th>
<th>Plasma concentration (µg/L)</th>
<th>Plasma half-life (days)</th>
<th>Estimated production rate (µg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.25-(OH)₂-D₃</td>
<td>0.03</td>
<td>1 to 3</td>
<td>1</td>
</tr>
<tr>
<td>24,25-(OH)₂-D₃</td>
<td>2</td>
<td>15 to 40</td>
<td>1</td>
</tr>
<tr>
<td>25-OH-D₃</td>
<td>20</td>
<td>5 to 20</td>
<td>10</td>
</tr>
</tbody>
</table>
Effects of 1,25-dihydroxycholecalciferol [1,25-(OH)₂ D₃] on calcium and phosphate metabolism.
Figure 8.41. Function and regulation of 1,25-(OH)$_2$D. (From Haussler and McCain, 1977.)
**Table 7.5 Causes of deficiency of 1:25-dihydroxy calciferol**

<table>
<thead>
<tr>
<th>Cause</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Failure to synthesize cholecalciferol in the skin</td>
<td>This occurs in dark-skinned people in a temperature climate</td>
</tr>
<tr>
<td>Dietary deficiency of cholecalciferol</td>
<td>(relatively unimportant)</td>
</tr>
<tr>
<td>Failure to hydroxylate cholecalciferol in the 25 position</td>
<td>This occurs in chronic liver disease; hepatic osteodystrophy</td>
</tr>
<tr>
<td>Rapid metabolism of cholecalciferol and its active metabolites</td>
<td>This occurs when hepatic enzymes are induced and is seen in patients taking anticonvulsants</td>
</tr>
<tr>
<td>Failure to hydroxylate 25-cholecalciferol in the 1 position</td>
<td>This occurs in patients with chronic renal failure; renal osteodystrophy</td>
</tr>
</tbody>
</table>
1. Required for the maintenance of normal sodium permeability in nerves
2. Involved in triggering the release of acetylcholine from nerve endings at the neuromuscular junction
3. Involved in excitation-contraction coupling in muscle cells
4. Serves as an intracellular signal for some hormones
5. Required by some enzymes for normal activity
6. Required for blood clotting to occur normally
7. Required for protein secretion
8. Constituent of bone
Table 21-1. Distribution (mmol/L) of calcium in normal human plasma.

<table>
<thead>
<tr>
<th>Diffusible</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Ionized (Ca²⁺)</td>
<td>1.18</td>
</tr>
<tr>
<td>Complexed to HCO₃⁻, citrate, etc</td>
<td>0.16</td>
</tr>
<tr>
<td>Nondiffusible (protein-bound)</td>
<td>1.16</td>
</tr>
<tr>
<td>Bound to albumin</td>
<td>0.92</td>
</tr>
<tr>
<td>Bound to globulin</td>
<td>0.24</td>
</tr>
<tr>
<td><strong>Total plasma calcium</strong></td>
<td><strong>2.50</strong></td>
</tr>
</tbody>
</table>

† Ionized Ca²⁺ concentration depends on blood pH. Alkalosis increases the protein-bound and decreases the ionized Ca²⁺ concentration, whereas acidosis has the opposite effect.
FIGURE 9-32. Effects of acid-base disturbances on plasma protein-binding of Ca$^{2+}$ and the ionized Ca$^{2+}$ concentration in blood.
<table>
<thead>
<tr>
<th>Constituent</th>
<th>Total Body Content Present in Bone (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium</td>
<td>99</td>
</tr>
<tr>
<td>Phosphate</td>
<td>85</td>
</tr>
<tr>
<td>Carbonate</td>
<td>80</td>
</tr>
<tr>
<td>Magnesium</td>
<td>50</td>
</tr>
<tr>
<td>Sodium</td>
<td>35</td>
</tr>
<tr>
<td>Water</td>
<td>9</td>
</tr>
</tbody>
</table>
Effects of calcitonin (CT) on calcium and phosphate metabolism.
Fig. 12.26 The principal actions of calcitonin and the factors thought to regulate its secretion.
Figure 1.2.25 The relationship between plasma calcium and PTH concentration.

- Plasma calcium (mmol/L): 3.0, 2.5, 2.0, 1.5
- Relative concentration of PTH or calcitonin

- Normal range
- Falling calcium, rising PTH, the secretion of parathyroid hormone
- Rising calcium, falling PTH, the secretion of calcitonin hormone

Note: The graph shows the inverse relationship between plasma calcium and PTH concentration.
Calcitonin

1. Calcitonin, a straight-chain peptide of 32 amino acids, has a molecular weight of 3400.

2. The biologically active core of the molecule probably resides in its central region.

3. Calcitonin is secreted by thyroid parafollicular cells known as "C" cells.

4. Calcitonin, (CT), decreases plasma calcium levels by antagonizing the actions of PTH on bone.

5. Calcitonin is also present in nervous tissue, where it may function as a neuromodulator.

6. The major stimulus to CT secretion is a rise in plasma calcium concentration.

7. The hypocalcemic action is caused by inhibition both of osteocytic osteolysis & osteoclastic bone resorption particularly when these are stimulated by PTH.

8. However, with respect to phosphate, it has the same net effect as PTH; that is, CT decreases plasma phosphate concentration & increases urinary phosphate excretion slightly.

9. The importance of CT in humans is controversial CT deficiency does not lead to hypercalcemia & CT hypersecretion does not produce hypocalcemia. It may be that abnormal CT secretion is easily compensated for by adjustment in PTH & vitamin D levels.

10. Is degraded within the liver & kidney, after half-life of 30-60 minutes.
Fig. 12.7  A diagram to illustrate the interactions of parathormone, calcitonin and vitamin D₃ and its derivatives in calcium homeostasis.
1. F, P, and Mg+ homeostasis are essential for health and life. A complex system acts to maintain normal body contents and levels of these minerals in the face of change.

2. The key elements in the system are:
   - Vit. D
   - PTH
   - Calcitonin
   - Kidneys
   - Intestinal absorption
   - Liver involvement in the homeostatic process
Table 21-2: Factors that affect bone formation and calcium metabolism.

<table>
<thead>
<tr>
<th>Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parathyroid hormone</td>
</tr>
<tr>
<td>1,25-Dihydroxycholecalciferol</td>
</tr>
<tr>
<td>Calcitonin</td>
</tr>
<tr>
<td>Glucocorticoids</td>
</tr>
<tr>
<td>Growth hormone and somatomedins</td>
</tr>
<tr>
<td>Thyroid hormones</td>
</tr>
<tr>
<td>Estrogens</td>
</tr>
<tr>
<td>Insulin</td>
</tr>
<tr>
<td>IGF-I</td>
</tr>
<tr>
<td>Epidermal growth factor</td>
</tr>
<tr>
<td>Fibroblast growth factor</td>
</tr>
<tr>
<td>Platelet-derived growth factor</td>
</tr>
<tr>
<td>Prostaglandin E₂</td>
</tr>
<tr>
<td>Osteoclast activating factor</td>
</tr>
</tbody>
</table>
Fig. 81-3. Integrated phosphate homeostasis. The responses to marked decreases of serum phosphate concentrations are shown; opposite responses occur to marked increases. (+ = stimulation; = inhibition; PTH = parathyroid hormone.)
Table 27-2
Some of the Physiological Actions of Phosphate

1. Functions as part of the intracellular buffer system
2. Important constituent of a variety of macromolecules, such as nucleic acids, phospholipids, metabolic intermediates, and phosphoproteins
3. Constituent of bone
Osteomalacia

Osteomalacia is rickets in adults and is frequently called "adult rickets."

Normal adults rarely have a serious dietary deficiency of vitamin D or calcium because large quantities of calcium are not needed for bone growth as in children. However, a serious deficiency of both vitamin D and calcium occasionally occurs as a result of steatorrhea (failure to absorb fat), for vitamin D is fat-soluble, and calcium tends to form insoluble soaps with fat; consequently, in steatorrhea both vitamin D and calcium tend to pass into the feces. Under these conditions an adult occasionally has such poor calcium and phosphate absorption that adult rickets can occur, though this almost never proceeds to the stage of tetany—but very often is a cause of severe bone disability.
<table>
<thead>
<tr>
<th>Causes of Osteomalacia and Rickets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inadequate availability of vitamin D</td>
</tr>
<tr>
<td>Defects in metabolic activation of vitamin D</td>
</tr>
<tr>
<td>Impaired action of 1,25-dihydroxycholecalciferol on target tissues</td>
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<td></td>
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</table>
RICKETS

Rickets occurs mainly in children as a result of calcium or phosphate deficiency in the extracellular fluid. Yet, ordinarily rickets is due to lack of vitamin D, rather than a dietary lack of calcium or phosphate. If the child is properly exposed to sunlight, the 7-dehydrocholesterol in the skin becomes activated by the ultraviolet rays and forms vitamin D₃, which prevents rickets by promoting calcium and phosphate absorption from the intestines, as discussed earlier in the chapter.

Children who remain indoors through the winter in general do not receive adequate quantities of vitamin D without some supplementary therapy in the diet. Rickets tends to occur especially in the spring months because vitamin D formed during the preceding summer is stored in the liver and is still available for use during the early winter months. Also, calcium and phosphate absorption from the bones can prevent clinical signs of rickets for the first few months of vitamin D deficiency.
OSTEOPOROSIS

Osteoporosis, the most common of all bone diseases in adults and especially in old age, is a different disease from osteomalacia and rickets, for it results from diminished organic matrix rather than abnormal bone calcification. Usually, in osteoporosis the osteoblastic activity in the bone is less than normal, and consequently the rate of bone deposition is depressed. But occasionally, as in hyperparathyroidism, the cause of the diminished bone is excess osteoclastic activity.
CAUSES OF OSTEOPOROSIS ARE:

1) Lack of physical stress on the bones because of inactivity.
2) Malnutrition to the extent that sufficient protein matrix cannot be formed.
3) Lack of vitamin C,
4) Postmenopausal lack of estrogen secretion.
5) Old age, in which many of the protein anabolic functions are poor.
6) Cushing's disease, because massive quantities of glucocorticoids cause decreased deposition of protein.
7) Acromegaly, possibly because of lack of sex hormones, excess of adrenocortical hormones, and often lack of insulin because of the diabetogenic effect of growth hormone.
**FIGURE 23-7** Signal transduction pathways activated by PTH or PTHrP binding to the hPTH/hPTHrP receptor. Intracellular cAMP is increased via Gs and adenylyl cyclase (AC). Diacylglycerol and IP$_3$ (1,4,5-InsP$_3$) are increased via Gq and phospholipase C (PLC). (Modified and reproduced with permission from McPhee SJ, Lingappa VR, Ganong WF [editors]: *Pathophysiology of Disease*, 4th ed. McGraw-Hill, 2003.)
MECHANISM OF ACTION

It now appears that there are at least three different PTH receptors. One also binds parathyroid hormone-related protein (PTHrP; see below) and is known as the hPTH/PTHrP receptor. A second receptor, PTH2 (hPTH2-R), does not bind PTHrP and is found in the brain, placenta, and pancreas. In addition, there is evidence for a third receptor, CPTH, which reacts with the carboxyl terminal rather than the amino terminal of PTH. The first two receptors are coupled to Gs, and via this heterotrimeric G protein they activate adenylyl cyclase, increasing intracellular cAMP. The hPTH/PTHrP receptor also activates PLC via Gq, increasing intracellular Ca\(^{2+}\) and activating protein kinase C (Figure 23-7). However, the way these second messengers affect Ca\(^{2+}\) in bone is unsettled.

In the disease called pseudohypoparathyroidism, the signs and symptoms of hypoparathyroidism develop but the circulating level of PTH is normal or elevated. Because the tissues fail to respond to the hormone, this is a receptor disease. There are two forms. In the more common form, a congenital 50% reduction of the activity of Gs occurs and PTH fails to produce a normal increase in cAMP concentration. In a different, less common form, the cAMP response is normal but the phosphaturic action of the hormone is defective.
Another protein with PTH activity, parathyroid hormone-related protein (PTHrP), is produced by many different tissues in the body. It has 140 amino acid residues, compared with 84 in PTH, and is encoded by a gene on human chromosome 12, whereas PTH is encoded by a gene on chromosome 11. PTHrP and PTH have marked homology at their amino terminal ends and they both bind to the hPTH/PTHrP receptor, yet their physiologic effects are very different. How is this possible when they bind to the same receptor? For one thing, PTHrP is primarily a paracrine factor, acting close to where it is produced. It may be that circulating PTH cannot reach at least some of these sites. Second, subtle conformational differences may be produced by binding of PTH versus PTHrP to their receptor, despite their structural similarities. Another possibility is action of one or the other hormone on other, more selective receptors.

PTHrP has a marked effect on the growth and development of cartilage in utero. Mice in which both alleles of the PTHrP gene are knocked out have severe skeletal deformities and die soon after birth. In normal animals, on the other hand, PTHrP-stimulated cartilage cells proliferate and their terminal differentiation is inhibited. PTHrP is also expressed in the brain, where evidence indicates that it inhibits excitotoxic damage to developing neurons. In addition, there is evidence that it is involved in Ca^{2+} transport in the placenta. PTHrP is also found in keratinocytes in the skin, in smooth muscle, and in the teeth, where it is present in the enamel epithelium that caps each tooth. In the absence of PTHrP, teeth cannot erupt.