Endocrine

PHARMACOLOGY

Title: Sheet 3 – Disorders of the Parathyroid Glands

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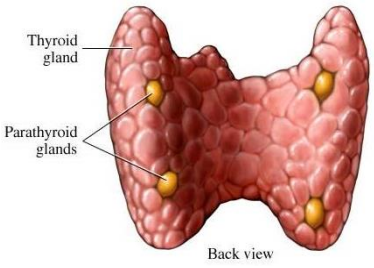
LEARNING OBJECTIVES

- *Describe the action and control of Parathyroid Hormone.*
- *Recognize the importance of Calcitonin and Vitamin D3.*
- *Understand the role of Calcitonin and Vitamin D3 in maintaining calcium homeostasis*
- *Describe the clinical uses of parathyroid hormone, calcitonin, vitamin D, and bisphosphonates.*
- *Identify some of the disorders related to the parathyroid glands.*

Parathyroid Hormone (PTH)



- The parathyroid glands are small endocrine glands (4 in number) that are found in the human neck and produce parathyroid hormone.

- **What stimulates the release of parathyroid hormone?**
  PTH is secreted from the parathyroid glands in response to a **low plasma concentration** of ionized (free) **calcium.**

- **What are the effects of parathyroid hormone**?
  1) PTH immediately causes the **transfer** of labile **calcium** stores from **bone into the blood stream**.
  2) PTH **increases** rates of dietary calcium **absorption** by the intestine **indirectly** via the vitamin D3 system activation of enterocyte activity.

- **Which hormones are responsible for maintaining homeostasis of Calcium, Magnesium and Phosphate in the body?**
  1) Parathyroid Hormone (**PTH**) ⟹ Polypeptide Hormone
  2) Calcitonin (**CT**) ⟹ Polypeptide Hormone
  3) 1,25-dihydroxycholecalciferol **($1,25(OH)_2D_3$)** ⟹ Sterol Hormone

- **How do PTH, CT, and $1,25(OH)_2D_3$ maintain homeostasis of the previously mentioned minerals?**
  These hormones regulate the flow of minerals in and out of the extracellular fluid compartments through their actions on **intestine**, **kidneys**, and **bones**

- The PTH acts **directly** on the ***bones*** and ***kidneys,*** and **Indirectly** on the ***Intestine*** through its effect on the synthesis of **$1,25(OH)_2D_3$**.
- Its production is regulated by the concentration of serum ionized calcium. **Lowering** of the serum **calcium** levels will **induce** an **increased** rate of **parathyroid hormone secretion**.

Calcitonin (CT)

- Calcitonin is the physiological **antagonist** of PTH. The two hormones act in concert to maintain normal concentration of calcium ions in the extracellular fluid.

- **What stimulates the release of calcitonin from the thyroid gland?**
  Calcitonin release is normally stimulated by **rising** serum **calcium levels.**

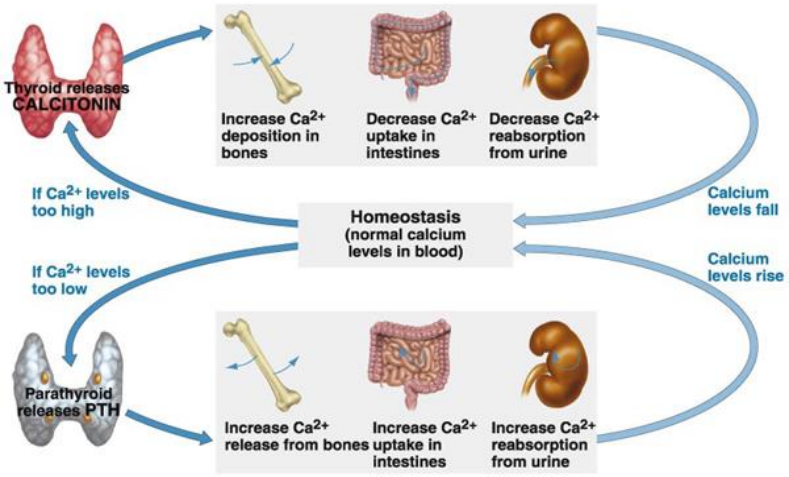
- **What suppresses/inhibits the release of calcitonin from the thyroid gland?**
  Hypocalcemia.

- **Which cells are responsible for the production and secretion of Calcitonin?**
  Calcitonin is released by the "C" cells (parafollicular cells in the thyroid gland)

- **What organs does calcitonin target**?
  Kidney & Bones.

- In a nutshell, the rising serum calcium level stimulates the release of calcitonin, which in turn brings calcium levels back to normal. Once calcium level in the blood is normal, calcitonin release is inhibited.

Make sure you understand this



VITAMIN D3 (CHOLECALCIFEROL)

- Vitamin D3, through its **active metabolite**, **1,25$(OH)_2D_3$**, also plays an important role in maintaining calcium homeostasis by:

  1. **Enhancing intestinal calcium absorption**
  2. **PTH-induced mobilization of calcium from bone**
  3. **calcium reabsorption in the kidney**

Clinical uses of parathyroid hormone, calcitonin, vitamin D, and bisphosphonates

1. Hyperparathyroidism

- Primary hyperparathyroidism is due to excessive production of PTH by one or more of hyperfunctioning parathyroid glands. This leads to hypercalcemia, which fails to inhibit the gland activity in a normal manner.
- The cause of primary hyperparathyroidism is unknown. A genetic factor may be involved (most common cause). The clonal origin of most parathyroid adenomas suggests a defect at the level of the gene controlling the regulation and/or expression of parathyroid hormone.
- **How can we treat hypercalcemia**?
  - **a)** In acute severe forms, the main stay of therapy is **adequate hydration** with **saline** and forced diuresis by **diuretics** to increase the urinary excretion of calcium rapidly, along with sodium and prevent its reabsorption by the renal tubules.
  - **b)** **Corticosteroids** are used to treat hypercalcemia, which is associated with hematological malignant neoplasms
  - **c)** **Mithramycin** is a toxic antibiotic which inhibit bone resorption. It is used to treat hypercalcemia, which is associated with hematological and solid neoplasms.
  - **d)** **Calcitonin** can also inhibit osteoclast activity and prevent bone resorption.
  - **e)** **Bisphosphonates** are used to prevent bone resorption. They are given IV or orally.
  - **f)** **Phosphate:** Oral phosphate can be used as an anti-hypercalcemic agent. It is commonly used as a temporary measure during diagnostic workup.
  - **g)** **Estrogen** can also be used to decrease bone resorption, and might be given to postmenopausal women with primary hyperparathyroidism using medical therapy
  - **h)** **Surgery:** Surgical treatment should be considered in all cases with established diagnosis of primary hyperparathyroidism (especially in hyperparathyroidism cases associated with malignancies). During surgery, the surgeon identifies all four parathyroid glands (using biopsy if necessary) followed by the removal of enlarged parathyroid or 3 ½ glands in multiple glandular disease.

2. Hypoparathyroidism

- Deficient secretion of PTH, which manifests itself **biochemically** by hypocalcemia, hyperphosphatemia diminished or absent circulating iPTH (intact PTH) and **clinically** by the symptoms of neuromuscular hyperactivity.
- **Treatment**: The mainstay of treatment is a combination of oral calcium with pharmacological doses of vitamin D or its potent analogues which induce calcium

absorption from the intestine. Phosphate restriction in the diet may also be useful with or without aluminum hydroxide gel, to lower serum phosphate level.

3. Osteoporosis

- **Postmenopausal osteoporosis** is the most common form of osteoporosis. In perimenopausal women, the greatest amount of bone density is lost during the first 5 year after onset of menopause.
- Women going through menopause at a particularly young age are especially at risk of developing osteoporosis.
- **Treatment: take some prophylactic regimen at the onset of menopause such as**:
  a) **estrogen replacement therapy** (ERT),
  b) **calcium supplementation**
  c) **Vitamin D3**.

  We mainly use these 2, as they can also increase bone density

  However, the benefits of ERT, including **increased bone density**, **decreased risk of colon cancer**, and **decreased vaginal atrophy** must be weighed against the slightly **increased risk of breast cancer, endometrial cancer**, **stroke**, and **deep vein thrombosis**.
  d) **ERT** appropriate combinations with a **progestin** negate such risk.

4. Paget's Disease

- Paget's disease is an uncommon disorder of bone characterized by mixed **lytic** and **sclerotic** bone changes.
- These individuals have areas of **increased bone resorption** and other areas of **abnormal new bone formation**.
- The abnormal bone formation can result in pain, deformity, and fracture of affected bones.
- The bisphosphonates and calcitonin are most commonly used in the treatment of this disease
- Bisphosphonates are given in a cyclic pattern to treat Paget's disease. Because Long-term continuous use of bisphosphonates can be associated with the induction of osteomalacia through a direct impairment of new bone formation.

5. Renal Osteodystrophy

- Patients with chronic renal failure develop **hyperphosphatemia** and **hypocalcemia**. The secondary hyperparathyroidism is due to hyperphosphatemia and decreased $1,25(OH)_2D_3$ formation.
- **Treatment**: **Oral** or **intravenous $1,25(OH)_2D_3$** (**calcitriol**) therapy along with **oral phosphate-binding agents** and **calcium supplementation.**