15.6.1.1: Thyroid and Parathyroids

The Thyroid Gland

The thyroid gland is a double-lobed structure located in the neck. Embedded in its rear surface are the four parathyroid glands. The thyroid gland synthesizes and secretes: thyroxine (T₄), and triiodothyronine (T₃) and calcitonin.

T₄ and T₃

Both hormones are derivatives of the amino acid tyrosine with four atoms of iodine in T₄, three in T₃. The thyroid secretes mainly (80%) T₄, but when T₄ enters target cells, one atom of iodine is removed from it converting it into T₃. T₃ is the more potent of the two hormones. It has many effects. Among the most prominent of these are:

- an increase in metabolic rate (seen by a rise in body temperature and the uptake of oxygen)
- an increase in the rate and strength of the heart beat

The thyroid cells responsible for the synthesis of T₄ and T₃ take up circulating iodine from the blood and attach them to tyrosine residues in the protein thyroglobulin. This action, as well as the synthesis of the hormones, is stimulated by the binding of thyroid stimulating hormone (TSH; also known as thyrotropin) to transmembrane receptors at the cell surface.

Diseases of the thyroid: Hypothyroid diseases - caused by inadequate production of T₃

- Cretinism: hypothyroidism in infancy and childhood leads to stunted growth and intelligence. Can be corrected by giving thyroxine if started early enough.
- Myxedema: hypothyroidism in adults leads to lowered metabolic rate and vigor. Corrected by giving thyroxine.
• **Goiter**: enlargement of the thyroid gland. Can be caused by:
  ◦ inadequate iodine in the diet with resulting low levels of T4 and T3
  ◦ an autoimmune attack against the thyroglobulin in the thyroid gland (called **Hashimoto's thyroiditis**)

Why should a hypothyroid disease produce an enlarged gland? The activity of the thyroid is under negative feedback control:
  ◦ The synthesis and release of thyrotropin releasing hormone (TRH) and TSH is normally inhibited as the levels of T4 and T3 rise in the blood.
  ◦ When the iodine supply is inadequate, T4 and T3 levels fall.
  ◦ This stimulates the hypothalamus and pituitary to **increased** TRH and TSH activity respectively. This stimulates the thyroid gland to enlarge.

• The symptoms of hypothyroidism can also result from **inherited mutations** in the genes encoding:
  ◦ the **receptor for TSH** (present on the surface of thyroid cells)
  ◦ the **receptor for T3** (present in the nucleus of almost all cells)

The T3 receptor is a nuclear protein bound to the **thyroid response element** in the promoters of the many genes whose expression is influenced by thyroid hormones. When its ligand, T3, binds to it, it becomes a transcription factor turning on the transcription of many genes.

Diseases of the thyroid: **Hyperthyroid diseases** - caused by excessive secretion of thyroid hormones

- **Graves’ disease**: Autoantibodies against the TSH receptor bind to the receptor mimicking the effect of TSH binding. Result: excessive production of thyroid hormones. Graves’ disease is an example of an autoimmune disease.

- **Osteoporosis**: High levels of thyroid hormones suppress the production of TSH through the negative-feedback mechanism mentioned above. The resulting low level of TSH causes an increase in the numbers of bone-reabsorbing osteoclasts resulting in osteoporosis.

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### Calcitonin

Calcitonin is a polypeptide of 32 amino acids. The thyroid cells in which it is synthesized have receptors that bind calcium ions (Ca^{2+}) circulating in the blood. A rise in its level, such as would occur with the absorption of calcium from a meal, stimulates the cells to release calcitonin. Calcitonin prevents a sharp rise in blood calcium by inhibiting the uptake of Ca^{2+} from the small intestine and inhibiting the Ca^{2+}-releasing activity of osteoclasts.

Because it slows the loss of Ca^{2+} from bones, calcitonin has been examined as a possible treatment for **osteooporosis**, a weakening of the bones that is a leading cause of hip and other bone fractures in the elderly. Being a polypeptide, calcitonin cannot be given by mouth (it would be digested), and giving by injection is not appealing. However, inhaling calcitonin appears to be an effective way to get therapeutic levels of the hormone into the blood. A synthetic version of calcitonin (trade name = Miacalcin) is now available as a nasal spray.
The Parathyroid Glands

The parathyroid glands are 4 tiny structures embedded in the rear surface of the thyroid gland. They secrete parathyroid hormone (PTH) a polypeptide of 84 amino acids. PTH increases the concentration of Ca\(^{2+}\) in the blood in three ways. PTH promotes

- release of Ca\(^{2+}\) from the huge reservoir in the bones. (99% of the calcium in the body is incorporated in our bones.)
- reabsorption of Ca\(^{2+}\) from the fluid in the tubules in the kidneys
- absorption of Ca\(^{2+}\) from the contents of the intestine (this action is mediated by calcitriol, the active form of vitamin D.)

PTH also regulates the level of phosphate in the blood. Secretion of PTH reduces the efficiency with which phosphate is reclaimed in the proximal tubules of the kidney causing a drop in the phosphate concentration of the blood.

Control of the Parathyroids

The cells of the parathyroid glands have surface G-protein-coupled receptors that bind Ca\(^{2+}\) (the same type of receptor is found on the calcitonin-secreting cells of the thyroid and on the calcium absorbing cells of the kidneys). Binding of Ca\(^{2+}\) to this receptor depresses the secretion of PTH and thus leads to a lowering of the concentration of Ca\(^{2+}\) in the blood. Two classes of inherited disorders involving mutant genes encoding the Ca\(^{2+}\) receptor occur:

- **loss-of-function mutations** with the mutant receptor always "off". Patients with these mutations have high levels of Ca\(^{2+}\) in their blood and excrete small amounts of Ca\(^{2+}\) in their urine. These mutations cause hyperparathyroidism.
- **gain-of-function mutations** with the mutant receptor always "on" (as though it had bound Ca\(^{2+}\)). People with these mutations have low levels of Ca\(^{2+}\) in their blood and excrete large amounts of Ca\(^{2+}\) in their urine. These mutations cause hypoparathyroidism.

Rare autoimmune disorders can mimic one or the other of these inherited disorders. In each case, autoantibodies bind to the receptors.

- If these inhibit the receptors, they cause hyperparathyroidism.
- If they activate the receptors (like those in Graves' disease), they cause hypoparathyroidism.

Diseases of the thyroid: Hyperparathyroidism

Tumors in the parathyroids elevate the level of PTH causing a rise in the level of blood Ca\(^{2+}\) at the expense of calcium stores in the bones. So much calcium may be withdrawn from the bones that they become brittle and break.

Until recently, treatment has been the removal of most — but not all — of the parathyroid tissue (i.e. the goal is the removal of 3 1/2 glands). Now clinical trials have begun on a drug (designated R-568) that mimics the action of calcium on the parathyroids, resulting in a drop in PTH and blood Ca\(^{2+}\) and sparing the calcium stores in the bone.
Diseases of the thyroid: Hypoparathyroidism

Causes:
- accidental removal of or damage to the parathyroids during neck surgery
- inherited mutations in the PTH gene
- inherited predisposition to an autoimmune attack against the parathyroids (and other glands)
- inherited defect in the embryonic development of the parathyroids (DiGeorge syndrome)

Treatment:
- give calcium supplements
- give calcitriol (1,25[OH]2 vitamin D3)
- give teriparatide (Forteo®), a synthetic (by recombinant DNA) version of PTH (containing only the 34 amino acids at the N-terminal).

For reasons that are not yet clear, this drug when given in daily injections (because it would be digested if taken by mouth), promotes strong bones and thus has been approved as a treatment for osteoporosis. While continuous high levels of PTH weaken bones by removing calcium from them, periodic injections of this drug strengthen bone by increasing the number and activity of osteoblasts.

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