

Chapter 134: Physiology

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Thyroid

History

The thyroid gland was recognized by Galen in the second century AD and goiter was treated empirically by feeding patients burned sponge during the twelfth and thirteenth centuries (Rolleston, 1936). Hyperthyroidism was described by Parry in 1786 and published in 1825. Ten years later Graves reported three cases. Hypothyroidism was described by Gull in 1873 and the functional significance of the thyroid was proven in 1882 after Kocher and Reverdin followed the courses of patients in whom they had performed total thyroidectomy. In 1891 Murray reported the first successful treatment in endocrinology by injecting thyroid extract into myxedematous patients (Sawin, 1990). Other physicians converted this therapy to oral administration of animal thyroid glands.

Anatomy

The human thyroid is associated with two additional endocrine glands, the parathyroids (usually having four lobes) and parafollicular cells, which are sparsely scattered throughout the parenchyma. The embryonal thyroid arises from the foregut (Gray and Skandalakis, 1972), the parathyroids from the third and fourth pharyngeal pouch, and the parafollicular cells from the neural crest (Pearse, 1976). Beginning in the second trimester of pregnancy thyroid follicles are present and hormone synthesis begins (Shepard, 1967).

Each lateral lobe of the adult human thyroid is smaller than the terminal phalanx of the adult thumb and closely attached to the trachea from the midlevel of the thyroid cartilage to the fifth and sixth tracheal cartilage. With the isthmus, the thyroid normally weighs 16 ± 6 grams (Pankow et al, 1985). It has an abundant blood supply and the gland is capable of enormous increases in size and in blood flow. It is overlaid by the thin strap muscles of the neck and irregularities of size or uniformity are readily apparent as a goiter.

The gland is composed of lobules containing clusters of closed follicles that are 30 to 500 microm in diameter. These follicles are the structural units of the gland and each is composed of a droplet of colloid that contains stored thyroglobulin (Tg). This is surrounded by a single layer of follicular epithelial cells that synthesize and utilize the thyroglobulin. The normal storage is sufficient for more than 1 month's requirement of thyroid hormone. To release the hormone, the follicular cells reincorporate the stored colloid by endocytosis and pinocytosis (Fig. 134-1). They hydrolyze the Tg and secrete thyroxin (T_4) with smaller quantities of triiodothyronine (T_3). The remaining fragments of hydrolysis are used for resynthesis of Tg.

Physiologic stimulants

The thyroid epithelial cells are under control of the anterior pituitary gland through thyroid-stimulating hormone (thyrotropine or TSH) (Magner, 1990), which is secreted from the anterior pituitary into the circulation. TSH binds to receptors on the basement membrane of the thyroid cells (Fig. 134-1) and this releases a second messenger, cyclic adenosine monophosphate (CAMP), within the follicular cells. All functions of the thyroid are stimulated by CAMP. The cells enlarge and develop numerous elongated microvilli at the apical edge, which invade the colloid storage. The accumulation of iodide, iodination, and synthesis of Tg are all stimulated. Endocytosis and hydrolysis of Tg are intensified, causing increased secretion of thyroid hormones. In addition, TSH causes increased blood flow and, usually, overall enlargement of the gland.

Thyroglobulin

To be functional, thyroglobulin must be iodinated. This occurs at the apical membrane interphase between the colloid and cells. At that point there is a concentration of iodide (iodide pump) and a unique enzyme thyroperoxidase (TPO), which catalyzes the iodination of Tg (DeGroot and Niepomniszcze, 1986). The iodinated Tg undergoes further rearrangement (ie, the coupling of two diiodotyrosines under the influence of TPO), as a result of which one to three molecules of tetraiodothyronine (thyroxine, T₄) are formed in peptide linkage in each molecule of stored thyroglobulin. In this form the stored hormone is inactive; it is activated only when the follicular cells ingest the Tg, hydrolyze it, and release the hormones to the blood (Fig. 134-1).

These details are clinically important because the pharmacologic agents used today interfere with specific steps; the antithyroid drugs propylthiouracil and methimazole prevent the TPO from iodinating thyroglobulin, C104⁻ and SCN⁻ block iodide concentration, and large doses of iodide (Lugol's solution) or lithium impair or prevent the release of the thyroid hormone. In addition, if follicles are damaged, Tg may be released and may appear in the serum in abnormal quantities. If epithelial cells are damaged, antibodies to the enzyme TPO will appear in the serum as antimicrosomal antibodies; these and antithyroglobulin are characteristic of Hashimoto's thyroiditis (DeGroot and Niepomniszcze, 1986).

Thyroid hormone

Transport: normal and abnormal

Thyroxin (T₄) is the primary transport form of the thyroid hormone and as such it is sometimes referred to as a prohormone. Normally 99.97% of serum T₄ and 99.7% of serum T₃ are firmly bound to the plasma proteins, thyroxin-binding globulin (TBG), prealbumin (or transthyretin), and albumin (Bartalena, 1990). These bound hormones are in dynamic equilibrium with the free T₄ and T₃. The concentration of TBG is increased in normal pregnancy and during estrogen therapy. Some drugs and uncommon pathologic states are associated with abnormal protein binding of thyroid hormones (Wenzel, 1981). The free T₄ and T₃ (FT₄ and FT₃) are

believed to be the effective forms of the hormones (Mendel, 1989) so concentrations of total serum T_4 and T_3 may be misleading indicators of clinical status. Concentrations of FT_4 and FT_3 are more meaningful than measures of total T_4 and total T_3 concentrations and practical methods are available to measure the free hormones (Ekins, 1990).

The binding of thyroid hormones to serum proteins is dramatically reduced during severe nonthyroid illness (NTI), (Fig. 134-2) (Brent and Hershman, 1986). Recently Poll et al (1990), suggested that tumor-necrosis factor (TNF or cachectin) may be a putative mediator of the NTI effect on thyroid-function tests. At present, it is important to recognize that the usual laboratory tests for thyroid functions are not valid during severe NTI.

Metabolism of thyroid hormone

Removal of the 5' iodine from T_4 by 5' deiodinase (5'DI) is necessary for maximum effectiveness of the hormone. The product, 3,3',5' triiodothyronine (T_3) is more than five times as effective as T_4 . However, if an inner ring iodine is removed by a different deiodinase (5 DI), the product, reverse T_3 (rT_3) has little or no hormone activity. Because of these metabolic pathways the effectiveness of thyroid hormone can be controlled by unique diiodinase enzymes in the peripheral tissues.

There are at least two (5'DI-I and 5'-DI-II) and their activities can be changed independently by drugs or by metabolic states. The hepatic and renal 5'DI-I accounts for most of the serum T_3 (Silva and Matthews, 1984). This deiodination is impaired by caloric restriction, subnormal levels of serum T_4 , or propylthiouracil. In contrast, the activity of 5'DI-II in the brain and the pituitary gland increases in the presence of low serum T_4 (Obregon et al, 1980; Silva and Larsen, 1968). Even more remarkable is the fact that Rt_3 in the cerebral cortex suppresses the 5'DI-II production of T_3 formation from T_4 and this reaction is the major source of T_3 in the cerebral cortex (Obregon et al, 1986). Overall, approximately 42% of the T_4 secreted by the thyroid is converted to T_3 and 34% to Rt_3 in peripheral tissues. The remaining 14% enters the bile as glucuronide and is excreted in the feces. Normally, less than 10% of the body T_3 is secreted by the thyroid gland as T_3 .

Feedback control

The hypothalamus, pituitary, and thyroid glands are controlled by a negative feedback system. The hypothalamus continually secretes a tripeptide, thyrotropin-releasing hormone (TRH) into the portal venous supply of the anterior pituitary. TRH maintains the responsiveness of the pituitary thyrotrophs and can change the glycosylation and biologic effectiveness of TSH (Mendes-Ferreira et al, 1986). The thyrotrophs deiodinate intrapituitary T_4 to pituitary T_3 , which inhibits the production and secretion of TSH by the thyrotrophs (Fig. 134-3) (Obregon et al, 1980). The half-life of TSH in blood is short (less than 1 hour); normally it shows a diurnal rhythm, with maxima near midnight that are approximately twice as great as the minima in the early afternoon (Brabant et al, 1990; Morley, 1981; Van Coevorden, 1989). The half-lives of T_3 (1 day) and T_4 (6 days) are much longer than for TSH and slight variations of serum T_3 and T_4

are not clinically relevant. Because of the central role of TSH in the maintenance of thyroid function, modern measurement of TSH is the best single criterion of thyroid function (Spencer et al, 1990); however, prolonged illness may reduce its diagnostic discrimination (Spencer et al, 1990).

Effects of thyroid hormones

The major biologic effects of thyroid hormones can be considered developmental or metabolic. The developmental effects are most dramatic in early life: body growth and brain development depend upon thyroid hormones. Specific nuclear receptors bind with T₃ and the combination activates or induces specific genes to produce mRNA (DeGroot et al, 1989). The transcription of these messengers produce proteins and enzymes that are essential for morphologic development of the central nervous system and production of essential growth and metabolic factors. T₃ also binds to mitochondria (Sterling, 1986), which may relate to the general stimulation of metabolism.

Hypothyroidism in the neonate, if untreated for the first 4 to 8 weeks, results in irreversible brain damage or cretinism (Bass, 1977). In adult hypothyroidism the basal oxygen utilization is reduced by 30% to 40%. Cerebration and muscular activity are impaired, normal temperature is not maintained, skin and hair become dry, and hepatic low-density lipoprotein (LDL) receptors are reduced (causing increased serum cholesterol). All these changes are reversible with treatment.

Excessive levels of thyroid hormones produce 20% to 100% increases in basal oxygen consumption, heat production, and sweating, with depletion of energy, fat, protein, and even calcium stores, despite increased food intake. The muscles become weak, the central nervous system becomes unstable and the patient exhibits tremors, anxiety, and mental confusion. The cardiac force, rate, and output are all typically increased. Characteristically, these effects from excessive thyroid hormones are all reversible within 1 to 6 months after blood thyroid hormone levels return to normal.

Autoimmune disease

During the past 30 years one of the most revealing advances in pathophysiology has been the demonstration that the serum of patients with Graves' disease and Hashimoto's thyroiditis contains thyrotropin receptor antibodies (TRAb). These are produced by lymphocytes within the thyroid (McKenzie and Zakarija, 1986; Rees-Smith, 1988). The antibodies bind to TSH receptors; those that continually stimulate the receptors are called *thyroid-stimulating immunoglobulins* (TSI) whereas those that block but do not stimulate the receptors are called *thyrotropin-binding inhibitors* (TBI). In either case, pituitary control of thyroid function is lost and persistent hyperthyroidism or hypothyroidism results.

The exophthalmos dermopathy associated with thyroid disease are believed to be of autoimmune origin but independent of the actions TSIs and TBIs (Jacobson and Gorman, 1984).

Parathyroid

Anatomy

Plate 17 (Cunningham, 1940) shows the typical anatomic relationships of the parathyroid glands. The inferior lobes develop with the thymus and therefore one or both may be located more caudally than shown and even within the thymus (Gray and Skandalakis, 1972). The parathyroids are well vascularized from branches of the inferior thyroid arteries.

Feedback control

Physiologically these small glands (total weight less than 0.15 g) produce the parathyroid hormone (PTH), which regulates the concentration of ionized calcium (Ca^{2+}) in the serum. Increased serum Ca^{2+} inhibits the release of PTH and decreased serum Ca^{2+} stimulates the secretion of PTH (Copp and Davidson, 1961; Patt and Luckhardt, 1942).

Biologically active hormone

PTH is synthesized as a large polypeptide with 115 amino acids (Habener and Potts, 1978), but before secretion it is fragmented into 84 amino acids. After secretion, the hormone is further fragmented into a species of 7000 daltons, which is biologically inactive, and another of 4000 daltons, which is biologically active. Radioimmunoassays for clinical measurement of PTH may use antibodies to different parts of the molecule. However, in most patients, each of the assays clearly differentiate hypercalcemia of hyperparathyroidism from hypercalcemia of malignancy (Lufkin et al, 1987).

Effect on bone

Today it seems paradoxical that the major effect of PTH on bone is stimulation of the phagocytic function of the osteoclasts, yet the osteoclasts have no receptors for PTH (Braidman et al, 1983). The osteoblasts have PTH receptors that are believed to communicate indirectly with the osteoclasts; by these processes, bone remodeling is continuously maintained (Rodan and Martin, 1981). Experimentally, calcitonin (Copp et al, 1962; Copp, 1967) from the parafollicular cells (C-cells) of the thyroid (Bussolati and Pearse, 1967) and from other neuroendocrine cells throughout the body (Becker et al, 1979) can inhibit osteoclasts (Chambers et al, 1984). The physiologic role of calcitonin in human beings is highly probable but as yet, unproven (Austin and Heath, 1981; Talmage and Meyer, 1976).

Effect on kidney and intestine

In addition to the effects on bone cells, PTH has unique effects on normal kidneys (Dennis et al, 1979). It stimulates resorption of Ca^{2+} from the distal tubules and inhibits phosphate absorption in the proximal tubules, thereby causing phosphate excretion. PTH also stimulates the normal kidneys to synthesize a highly active hormone, 1,25-dihydroxycalciferol

(calcitriol), from calcidiol, derived from hepatic metabolism of cholecalciferol (vitamin D3). Without calcitriol nearly all of the dietary Ca^{2+} would be unabsorbed and excreted in the feces. However, calcitriol induces intestinal mucosal cells to synthesize calcium-binding protein (CaBP), which retains calcium (Wasserman and Taylor, 1966) and functions in the transfer of dietary calcium from the intestine into the serum. The increased serum Ca^{2+} then downregulates PTH secretion and maintains homeostasis (Fig. 134-4) (DeLuca, 1985). Calcitriol also functions together with PTH to stimulate bone Ca^{2+} mobilization and is essential for normal bone development and growth.

In the absence of PTH or during severe renal damage, Ca^{2+} is inadequately absorbed because of calcitriol deficiency; serum phosphate increases and hypocalcemic tetany results. In hypoparathyroidism this distressing syndrome is reasonably controlled by the administration of calcitriol in carefully managed doses that permit dietary Ca^{2+} to be absorbed adequately.

Population screening

At the present time, population screening for parathyroid disease by radioimmune assay for PTH is not reasonable, but screening population for elevated levels of ionized Ca^{2+} in serum has resulted in the discovery of more than 250 new cases of primary hyperthyroidism per million per year (Heath et al, 1980; Mundy et al, 1980).