Endocrinology – thyroid

Rudolf Cardinal, 18 Oct 98

The thyroid

The thyroid is butterfly-shaped, having two lateral lobes and a central pyramidal lobe. Very vascular. Thyroid tissue contains **follicles** which are surrounded by cuboidal epithelium – the **follicular cells.** The follicular cells make the principal thyroid hormone, **thyroxine.** Scattered in and around the follicles are **parafollicular or clear (C) cells.** The C cells make **calcitonin** (see handout on calcium). Don't confuse the thyroid with the *parathyroid glands* (which make PTH, see handout on calcium).

Embryology. The thyroid derives from the pharynx, which is why remnants can turn up in the tongue (a lingual thyroid). It is therefore embryologically *exocrine*. It migrates down to lie in front of the trachea, just below the cricoid cartilage. The C cells have a different origin in neural crest tissue.

Thyroid hormones – thyroxine (T_4) and triiodothyronine (T_3)

Nature and synthesis

- Thyroid hormones contain **iodine.** Terrestrial vertebrates don't get much, so the thyroid is adapted to trap it.
- Iodide is trapped and transported into follicular cells, then excreted into the lumen of the follicle. The cell also makes **thyroglobulin (TG)** and exocytoses this into the lumen. The iodide (I^-) is oxidised by a peroxidase on the luminal surface of the cell. The resulting free iodine (I) reacts **non-enzymatically** with tyrosine residues of the thyroglobulin in the follicle, a process called **iodination.** This forms mono- and diiodotyrosine residues (MIT, DIT), which are **coupled** together, possibly by the same peroxidase, to form mainly **thyroxine (T_4)** and some **3,5,3'-triiodothyronine (T_3)**. This process may be catalysed by the peroxidase, but is certainly helped by the structure of the thyroglobulin molecule.
- The follicle contains a **colloid** of thyroglobulin with MIT, DIT, T_4 and T_3 on it. There are no cells within the follicle.
- The follicles may be used to store thyroid hormones. Next, the colloid is pinocytosed back into the cell and the thyroglobulin is split off by proteolysis to leave the free hormone in vesicles that may be exocytosed into the circulation. MIT and DIT that is taken up is recycled within the cell.
- Thyroid hormones are **water-insoluble,** like steroids, so they require specific carrier/binding proteins in the plasma (and in the cell cytosol, to gain access to the nucleus). Thyroxine binds to **thyroxine-binding prealbumin (TBPA)** and **thyroxine-binding globulin (TBG),** especially the latter, which carries 75% of all T_4 and T_3. It also binds to **albumin;** though the affinity is very low, there's so much albumin around that it carries a fair amount of thyroid hormone. Only about 0.5% of the serum T_4 and 0.3% of the T_3 is in the free state, but this is the physiologically active form (see below). Half-lives: T_3 about 1.3 days, T_4 about 7 days.

Mode of action

- Thyroid hormones act on **nuclear T_3/T_4 receptors** to regulate gene transcription. (Subsequent effects include activation of the Na^+/K^+ pump, increased mitochondrial respiration and possible increased β-adrenoceptor synthesis[1].)
- **T_3 versus T_4.** Much more T_4 is secreted than T_3 (ratio ~30:1). However, most T_4 is monodeiodinated to T_3 in the periphery. In fact, about 85% ends up as T_3. T_3 is the major physiologically active thyroid hormone, but T_4 may have important developmental roles.
- **Reverse T_3 (rT_3).** This is a structural isomer of T_3 that is **inactive** as a hormone – see "Control", below.

Functions

- **Not essential for life.** Was originally thought so, but those operations had removed the parathyroid (q.v.).
- Thyroid hormones have a **general stimulating effect on metabolism.** They affect nearly every cell in the body. They promote thermogenesis, via the actions on the sodium pump and mitochondrial activity. An optimal level promotes protein synthesis (i.e. deficiency/excess impairs it). All aspects of lipid metabolism are stimulated. Carbohydrate metabolism is also stimulated: intestinal absorption and glucose uptake by adipose tissue are stimulated (an effect that potentiates insulin), while the hyperglycaemic/glycogenolytic effects of adrenaline are potentiated and insulin degradation is increased (reducing insulin sensitivity).
- **Growth and development.** Required for normal maturation of bone and CNS, for fetal lung surfactant production and for milk secretion. See also section on disease, below.
- **Permissive actions.** Required for the actions of other hormones on target tissues, probably because thyroid hormones induce the synthesis of proteins that the other hormones act on.

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[1] Apparently this is disputed. However, clinical relevance: the β-blocker propranolol improves many manifestations of hyperthyroidism.

Control

- **TSH** from the pituitary stimulates thyroid hormone secretion via a plasma membrane receptor on the follicular cell.
- **TRH** from the hypothalamus stimulates TSH release.
- **Negative feedback.** Thyroid hormones inhibit both hypothalamic TRH and pituitary TSH secretion.[2]
- **Tissue regulation.** During fasting, peripheral tissues make less T_3 and more rT_3. So the less glucose is available, the less T_3 is created and the less the cell's metabolism is stimulated. High carbohydrate intake increases T_3 levels, which increases diet-induced thermogenesis. Low-carbohydrate diets have the opposite effect. This could be an adaptation to allow the organism to eat enough to obtain scarce nutrients (e.g. protein) without being burdened with a weight gain.
- Stress inhibits TSH secretion. In many mammals, including infant but perhaps not adult humans, exposure to cold causes rapid TSH release.
- **Learn and Remember** – it's the *free* hormone level that matters. For example, TBG levels double in pregnancy, so free T_4 levels initially fall, but the feedback systems ensure increased T_4 synthesis as a result. The system will equilibriate around a new level with almost double the total T_4 present, but the same free concentration as before. *This applies to many hormones and other protein-bound electrolytes that you will come across, and it is vital that you understand this principle.*

Disease – syndromes

- Deficiency in adults → **hypothyroidism,** a.k.a. myxoedema (*myxa* mucus, *oidema* swelling – a mucinous protein is deposited subcutaneously because mucopolysaccharide metabolism impaired). Sluggish, slow reflexes, 'peaches and cream' complexion, sensitive to cold, low basal metabolic rate, decreased cardiac output and heart rate, impaired intestinal glucose absorption, high plasma cholesterol, overweight. In women, menorrhagia and impaired fertility.
- Deficiency in children → **cretinism.** This has all the features of adult hypothyroidism, but also severe growth retardation and intellectual impairment. (Bone elongation and maturation is impaired – GH secretion is diminished; thyroid hormones are required for the action of GH; other effects as well. CNS maturation impaired.) Characteristic appearance: facial bone development retarded, but tongue still grows so it appears too large for the mouth.
- Excess in adults → **hyperthyroidism,** a.k.a. thyrotoxicosis. Restless, irritable, thin, high BMR, increased catabolism, high CO/HR, low cholesterol, etc. A severe hyperthyroid crisis ("thyroid storm") is dangerous – cardiac arrhythmias.

Disease – iodine

- **Iodine deficiency** causes thyroid hypertrophy and **goitre.**[3] Iodine deficiency → decreased thyroid hormone synthesis → increased TSH → follicular cell hypertrophy and hyperplasia.
- Certain **drugs** can inhibit iodide transport (e.g. thiocyanates). After a while, this causes thyroid hypertrophy and goitre. Some plants contain *cyanogenic glucosides* (apricots, cherries, almonds, cassava, sweet potato) or *thioglucosides* (the *Brassica* family – cabbages, Brussels sprouts, cauliflowers etc.), both of which are metabolised to thiocyanates. These plants are therefore **dietary goitrogens,** and may be responsible for *endemic goitre* in parts of the world (esp. where cassava is a staple food). Other drugs can inhibit different synthetic steps. Even **iodine** is transiently inhibitory to thyroid function in large doses – mechanism unknown.

Disease – neoplasia and autoimmunity

Many, but note the following:

- Hypothyroidism may be due to thyroid disease (primary hypothyroidism) or pituitary disease (secondary). *How would you distinguish the two?*
- **Tumours** in the thyroid may be inactive or active; if they are active they may cause hyperthyroidism.
- **Graves' disease** is an autoimmune disease, in which antibodies are made to the TSH receptor. The antibodies have the property of mimicking the action of TSH, so stimulate the thyroid and cause hyperthyroidism. The *exophthalmos* (protrusion of the eyes) is not a feature of the hyperthyroidism, but of an autoimmune-mediated infiltration behind the eye. See a picture and you'll never forget.

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[2] T_4 has more hypothalamic action and T_3 inhibits the pituitary.

[3] Once known as "Derbyshire neck" – this area was historically deficient in iodine. Cretinism due to iodine deficiency is still a major problem in parts of the world.