



# **College of Pharmacy**

## **Fifth Stage**

### **Clinical Chemistry**

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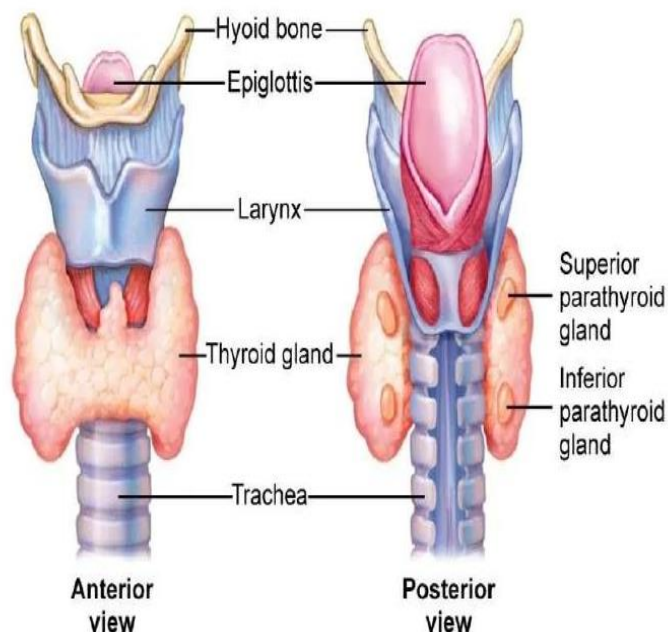
**Lectutre 4**

**Thyroid Gland**

# Thyroid Gland

The thyroid gland secretes three hormones: thyroxine ( $T_4$ ) and triiodothyronine ( $T_3$ ), both of which are iodinated derivatives of **tyrosine**. The third hormone is **calcitonin**. The  $T_4$  and  $T_3$  are produced by the follicular cells but calcitonin is secreted by the C cells (parafollicular cells). About 10 times more  $T_4$  than  $T_3$  is formed, with most of the  $T_3$  being formed by **de-iodination** in the peripheral tissues liver, kidneys and muscle.

Some of the circulating  $T_4$  is de-iodinated by enzymes in peripheral tissues, especially in the liver and kidneys. About 80 per cent of the plasma  $T_3$  is produced by the removal of an iodine atom from the outer ( $\beta$ ) ring; the remaining 20 per cent is secreted by the thyroid gland. De-iodination of the inner ( $\alpha$ ) ring produces **reverse  $T_3$** , which is probably **inactive**. The  $T_3$  binds more avidly to thyroid receptors than  $T_4$  and is the main active form.

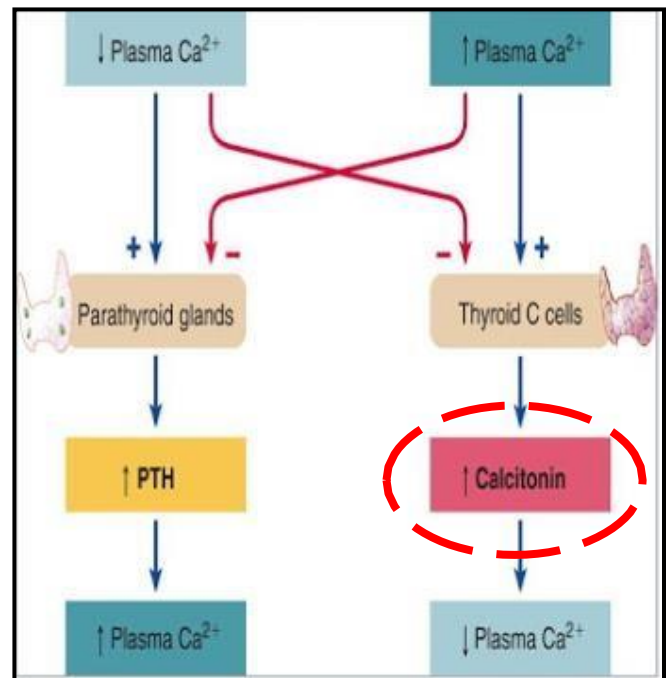
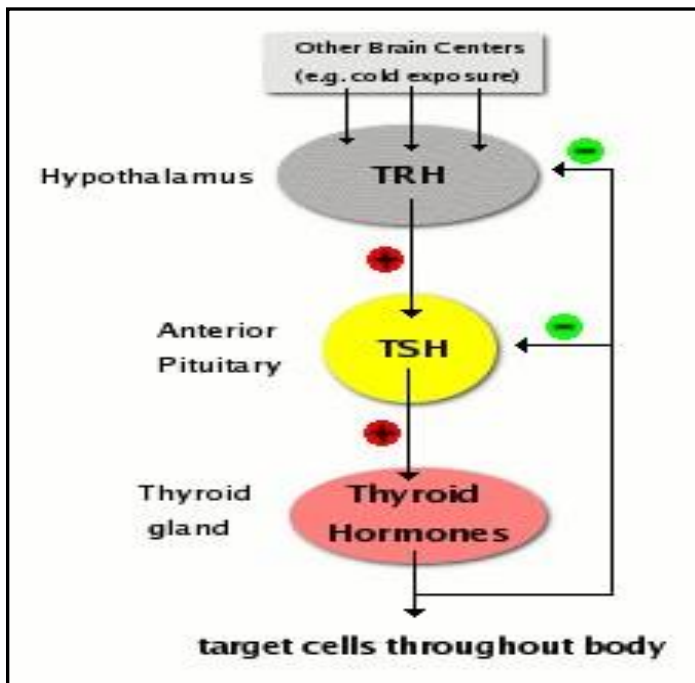


## Action of thyroid hormones

Thyroid hormones affect many metabolic processes, increasing oxygen consumption. They bind to specific receptors in cell nuclei and change the expression of certain genes. Thyroid hormones are essential for normal growth, mental development and sexual maturation and also increase the sensitivity of the cardiovascular and central nervous systems to catecholamines, thereby influencing cardiac output and heart rate.

## Control of thyroid-stimulating hormone secretion

Thyroid-stimulating hormone (TSH) which is a pituitary trophic hormone stimulates the synthesis and release of thyroid hormones from the thyroid gland. TSH secretion from the anterior pituitary gland is controlled by thyrotrophin-releasing hormone (TRH) from the hypothalamus and also controlled by negative feedback by the circulating concentrations of thyroid hormones.



## Protein binding of thyroid hormones in plasma

Most of the plasma  $T_4$  and  $T_3$  is protein bound, mainly (70 per cent) to an  $\alpha$ -globulin, **thyroxine-binding globulin (TBG)**, and, to a lesser extent (15 per cent), **transthyretin (previously called pre-albumin)**, with about 10–15 per cent bound to **albumin**. In keeping with many other hormones, the **free** unbound fraction is the physiologically **active** form, which also regulates TSH secretion from the anterior pituitary. Modern laboratory assays tend to measure the free hormones. Changes in the plasma concentrations of the binding proteins, particularly TBG, alter plasma total  $T_4$  and  $T_3$  concentrations, **but not** the concentrations of **free hormones**.

## Thyroid function tests (TFT)

Laboratory tests of thyroid function are required to assist in the diagnosis and monitoring of thyroid disease. Assessment of thyroid hormone secretion can be made by measuring plasma TSH as well as either  $fT_4$  or total  $T_4$  [sometimes also free  $T_3$  ( $fT_3$ ) or total  $T_3$ ]. Each test has its advantages and disadvantages, although probably most laboratories now offer  $fT_4$  and  $fT_3$  assays rather than total hormone concentrations. **Plasma TSH assays** are used as **first-line** assays for thyroid function assessment.

- 1- Plasma thyroid-stimulating hormone (TSH).
- 2- Plasma total thyroxine (Total  $T_4$ ) or free thyroxine ( $fT_4$ ) assays.
- 3- Plasma total tri-iodothyronine (Total  $T_3$ ) or free tri-iodothyronine ( $fT_3$ ).
- 4- Thyrotrophin-releasing hormone test (TRH test).
5. Other tests of thyroid function include measurement of various antibodies such as
  - A) Thyroid-stimulating immunoglobulin (TSI) antibodies that bind to and stimulate the TSH receptor (Graves' disease).
  - B) Anti-thyroid peroxidase (anti TPO), anti-thyroglobulin (anti-Tg) or TSH receptor blocking antibodies.

## Drug effects on thyroid function tests

Drugs may alter plasma  $T_4$  and  $T_3$  concentrations as appeared in Table 1

Table 1 Drug effects on thyroid function tests

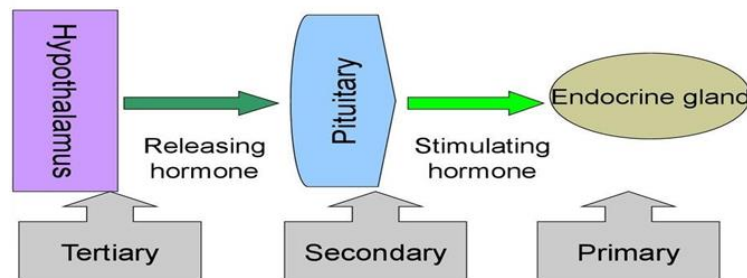
Drug	$T_4$	$fT_4$	$T_3$	$fT_3$	Remarks
Amiodarone	↑	Normal or ↑	Normal	Normal	Blocking $T_4$ to $T_3$ conversion
Androgens	↓	Normal	↓	Normal	Reduced TBG
Carbamazepine	↓	↓	Normal	Normal	Increased $T_4$ to $T_3$ conversion
Carbimazole	↓	↓	↓	↓	Therapeutic if thyrotoxic
Lithium	↓	↓	↓	↓	Lithium may inhibit iodination
Estrogens	↑	Normal	↑	Normal	Increased TBG
Phenytoin	↓	↓	Normal	Normal	Increased $T_4$ to $T_3$ conversion
Propranolol	Normal	Normal	↓	↓	Blocking $T_4$ to $T_3$ conversion
Propylthiouracil	↓	↓	↓	↓	Therapeutic if thyrotoxic
Salicylate	↓	Normal	↓	Normal	Reduced TBG binding
Some radiocontrast media	↑	Normal	↓	Normal or ↓	Blocking $T_4$ to $T_3$ conversion (transient effect)

$T_4$ , thyroxine;  $T_3$ , tri-iodothyronine;  $fT_4$ , free thyroxine;  $fT_3$ , free tri-iodothyronine; TBG, thyroxine-binding globulin.

## Interference of assays by immunoglobulins

Anti- $T_4$  or anti- $T_3$  immunoglobulins or heterophilic antibodies (induced by external antigens, e.g. derived from other species that cross-react with self-antigens) can cause a spurious elevation of  $T_4$  or  $T_3$  (or free hormones), respectively, when assayed by immunoassay. This needs to be remembered when interpreting thyroid function test results.

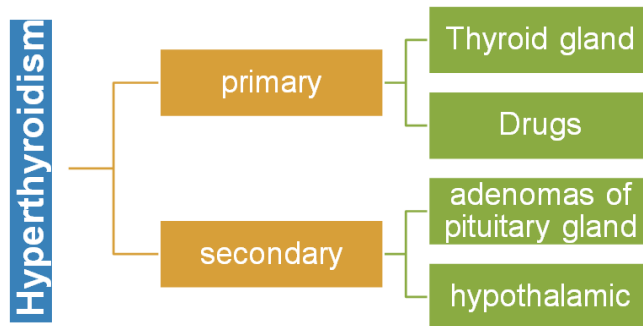
## The levels of disorders



## Disorders of the thyroid

### Hyperthyroidism (thyrotoxicosis)

Hyperthyroidism causes **sustained high** plasma concentrations of  $T_4$  and  $T_3$ . The plasma  $fT_4$  and  $fT_3$  concentrations are clearly high and the TSH concentration is suppressed in clinically thyrotoxic patients.



There is often **generalized increase** in the metabolic rate, evidenced clinically by, for example, heat intolerance, a fine tremor, tachycardia including atrial fibrillation, weight loss, tiredness, anxiety, sweating and diarrhoea.

### Graves' disease

This is the most common form of thyrotoxicosis and occurs more often in females than in males. It may be caused by relatively autonomous secretion from a diffuse goiter. It is an **autoimmune** thyroid disease characterized by a variety of circulating antibodies.

### Hypothyroidism

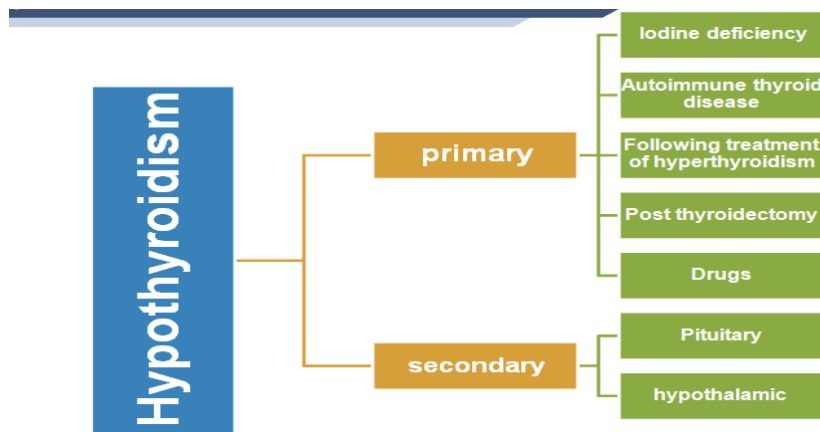
Hypothyroidism is caused by **suboptimal** circulating concentrations of thyroid hormones. It becomes more prevalent with age, affecting about 6 per cent of people over 60 years, and is more common in women.

**Raised plasma TSH and low  $fT_4$  concentrations suggest primary hypothyroidism.** The thyroid antibodies should be measured and, if positive, other autoimmune diseases excluded.

Low plasma TSH and low fT<sub>4</sub> concentrations may indicate that the hypothyroidism is caused by a hypothalamic or pituitary disorder. A TRH test should be done, if indicated, and the pituitary gland assessed.

The most common cause of hypothyroidism worldwide is iodine deficiency. In areas of adequate iodine intake, acquired hypothyroidism is mainly due to autoimmune thyroiditis or Hashimoto's thyroiditis, which is more frequently seen in women and the elderly. About 90 per cent of patients have positive thyroid antibodies, for example anti-thyroid peroxidase (anti TPO), anti-thyroglobulin (anti-Tg) or TSH receptor blocking antibodies.

Hashimoto's thyroiditis, an autoimmune condition, has been mentioned as a cause of hypothyroidism.



The condition may develop insidiously and in its early stages may cause only vague symptoms. There is a generalized slowing down of metabolism, with lethargy, bradycardia, depression and weakness. If the hormone deficiency is caused by a primary disorder of the thyroid gland, the patient may present with weight gain, myopathy, menstrual disturbances, such as menorrhagia, and constipation. The skin may be dry, the hair may fall out and the voice may be hoarse. Subcutaneous tissues are thickened; this pseudo-oedema, with a histological myxoid appearance, accounts for the term myxoedema, which is sometimes used to describe advanced hypothyroidism. In severe cases, coma with profound hypothermia may develop.

**Goiter:** enlargement of the thyroid, can occur in patients with hyperthyroidism, hypothyroidism and euthyroid individuals (euthyroid goiter).

### Interpretation of thyroid function tests (TFT)

