MEDICAL PRACTICE

Scientific Basis of Clinical Practice

Thyroid Physiology

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The thyroid develops from the endoderm in the floor of the pharynx and migrates downwards, anterior to the primitive gut. Faults in the process cause thyroglossal cyst and fistula and the presence of thyroid tissue in abnormal situations, such as the posterior part of the tongue and retrosternally. In mammals the thyroid also contains cells derived from the last branchial pouches, the parafollicular cells which secrete calcitonin. In this article the term thyroid hormones does not include calcitonin.

Iodine Metabolism and Simple Goitre

Iodine is essential for the synthesis of the thyroid hormones as it forms 65% of the product that is released into the blood stream. This appears to be the only physiological role of iodine. Man requires 0.1 mg per day to replace the iodine lost from the body, mainly in the urine, an amount which can be obtained by eating two average servings of sea fish a week. The other main dietary sources of iodine are milk and eggs, but these contain little when produced in those inland areas where water and soil are deficient in the element. In many countries potassium iodide is added to table salt. This has been recommended in Britain¹ but has never been enforced by legislation.

It is not known whether an inadequate intake of iodine is responsible for any cases of sporadic goitre in Britain. In 16 out of 21 cases of non-toxic goitre investigated by Koutras and his colleagues² the concentration of inorganic iodide in the plasma and the amount excreted in the urine were less than in control subjects. It was concluded that an inadequate intake of iodine may have been the cause. Simple goitres occur in a large proportion of pregnant women. Some of these goitres may be

due to iodine deficiency resulting from the increased iodide clearance which occurs during pregnancy.³

Goitrogenous chemicals interfere with the organic binding of iodine. As in iodine deficiency, lack of thyroid hormone stimulates overproduction of thyroid-stimulating hormone (TSH), which causes hypertrophy and hyperplasia of the gland. Though dietary goitrogens have not been shown to be a cause of sporadic goitre in Britain, possibly they are responsible for some cases. On the other hand, several drugs—for example, para-amino-salicylic acid, phenylbutazone, and thiouracil—are goitrogenic.

Synthesis and Release of Thyroid Hormones

In the alimentary tract dietary iodine is converted into iodide which is readily absorbed from the stomach and upper part of the small intestine. Iodide is concentrated within the thyroid and several other tissues. Normally in man the thyroid/serum iodide ratio is about 50/1 but increases up to 400/1 during treatment with antithyroid drugs. The iodine pump mechanism is located in the peripheral border of the follicular cells.

The thyroid contains very little free iodide because iodide is very rapidly oxidized to nascent iodine, a reaction depending on a peroxidase enzyme system in the follicular cells. The active iodine then combines with residues of the amino-acid tyrosine in the thyroglobulin (TGB) at the periphery of the follicles (Fig. 1.)

The compounds formed by the iodination of tyrosine are moniodotyrosine (MIT) and diiodotyrosine (DIT). Thyroxine (T-4) is formed by the coupling of pairs of DIT molecules, and triiodothyronine (T-3) by the coupling of MIT and DIT molecules. During synthesis and subsequent storage in the colloid T-4 and T-3 are bound to thyroglobulin. The first stage in the release of the hormones is the passage of droplets of colloid from the periphery of the follicles into the follicular cells by pinocytosis. The hormones are liberated by the action of a proteinase system, which hydrolyses the peptide linkages of the thyroglobulin, and are then released into the circulation.

FIG. 1—Steps in the synthesis and release of thyroid hormones affected by TSH (For meanings of abbreviations see text.)

Antithyroid Drugs

Potassium perchlorate reduces the uptake of iodine, but perchlorate, like the thiourea derivatives, may cause agranulocytosis and aplastic anaemia.

Carbimazole, propylthiouracil, and methylthiouracil inhibit the oxidation of iodide to iodine by competing with iodide as a substrate for peroxidase.⁴ These drugs also appear to interfere with the iodination of tyrosine and the coupling of iodotyrosines but do not affect the mechanism of secretion. Secretion diminishes after a latent period, during which the colloid becomes depleted of hormone.

Thyroid secretion is reduced by pharmacological doses of iodide because, in high concentration, this ion inhibits the proteolytic enzyme system involved in the release of hormone.⁵ Unfortunately, the effect wears off after about two weeks, probably because the iodide concentrating mechanism is also impaired. Iodine treatment has reduced the danger of partial thyroidectomy for thyrotoxicosis and is of value in the management of thyrotoxic crisis.

During radioiodine treatment there is little penetration of the beta radiation from the thyroid into surrounding tissue. Nevertheless, the gonads receive a small amount of radiation from circulating radioiodine and the possibility of genetic damage makes this form of treatment unsuitable for patients under 45 years of age.

Control of Thyroid Activity

The most important regulator of thyroid function, thyroid-stimulating hormone (TSH), rapidly increases the rates of release and synthesis of thyroid hormones and stimulates the growth of the gland. The increase in secretion is almost immediate and is due to activation of the proteinase system responsible for the hydrolysis of thyroglobulin. There is an increase in the uptake of iodine after a latent period, in man, of about eight hours. There is now much evidence to support the hypothesis that, after binding to follicular cells, TSH activates adenyl cyclase, the enzyme involved in the formation of cyclic 3', 5'-AMP. The latter then stimulates iodine trapping, iodination of tyrosine, iodothyronine synthesis, and release of the thyroid hormones.⁶

The activity of the TSH-secreting basophil cells in the adenohypophysis is controlled in two ways. Thyrotrophin releasing factor (TRF) stimulates release and probably synthesis of TSH. In common with the other hypophysiotrophic hormones controlling adenohypophyseal function, TRF is secreted in the hypothalamus and reaches the adenohypophysis via the pituitary portal vessels. High levels of thyroxine and triiodothyronine in the circulation reduce the secretion of TSH.

The secretion of thyroid hormones is influenced indirectly by factors controlling TRF production. Probably the concentrations of free thyroid hormones in the circulation affect not only the pituitary but also the hypothalamus, which apparently responds to low levels of T-3 and T-4 by increasing the output of TRF.⁷ TRF secretion is also increased by exposure to cold.

Long-acting Thyroid Stimulator

Initially, it was thought probable that the hyperthyroidism of Graves's disease was associated with excessive production of TSH. Nevertheless, reports of Graves's disease occurring in hypopituitarism and the equivocal results of early measurements of serum TSH in patients with Graves's disease suggested that this might not be so.⁸ After the introduction of a bioassay method for TSH which depends on the release of radioactive hormones from the assay animal's thyroid, sera from a large proportion of patients with Graves's disease were shown to produce a response whose peak occurred later than that produced by TSH.⁹ The substance responsible for the delayed peak, long-acting thyroid stimulator (LATS), has since been shown to be chemically and immunologically distinct from TSH. LATS is a 7S gammaglobulin which can be synthesized in vitro by lymphocytes from some patients with Graves's disease.¹⁰ Though it has many characteristics of an antibody the relevant antigen has not been identified. LATS appears to play a part in the pathogenesis of pretibial myxedema, but there is no evidence that it is directly responsible for the eye lesions of Graves's disease; neither has it been established that these are due to an exophthalmos-producing substance from the hypophysis.⁸

Thyroid Hormones in the Circulation

Over 99% of the thyroxine and triiodothyronine in the blood are bound to protein, mainly to thyroxine-binding globulin (TBG). The serum protein-bound iodine level (PBI) is a measure of this fraction and is a valuable index of thyroid function—though it does not measure the physiologically active, unbound hormones. The concentration of free T-4 in the circulation is about three times that of T-3. However, the potency of T-3 is greater, so that the physiological activity of the amounts of the two hormones present in the circulation is similar. Recently it has been shown that some of the plasma T-3 is formed by extrathyroidal conversion of T-4 to T-3.¹¹ This raises the question whether T-4 itself is able to stimulate cells or whether it must first be transformed to T-3 by the peripheral tissues.

The concentrations of the thyroid hormone-binding proteins in the plasma can alter independently of the levels of free T-4 and T-3. Androgens reduce and oestrogens increase the binding proteins. Consequently the serum PBI level is raised in euthyroid pregnant women and in women taking oral contraceptives.

Actions of Thyroid Hormones

OXYGEN CONSUMPTION

The effects of thyroid disease on basal oxygen consumption have been known for a long time. Though it is probable that the site

of action of the thyroid hormones on respiration is the mitochondrion, their mode of action is not understood. Until recently it was thought that the thyroid hormones controlled cellular respiration by uncoupling oxidative phosphorylation, but this and the associated swelling of mitochondria are now believed to be pharmacological, and not physiological, effects.¹²

PROTEIN SYNTHESIS

As the calorogenic action of thyroxine is blocked by small doses of actinomycin,¹³ the effect of the thyroid hormones on metabolic rate may be secondary to an action on protein synthesis. Both T-4 and T-3 increase the incorporation of amino-acids into mitochondrial protein,^{14 15} and it has been suggested that the thyroid hormones may have a primary action on mitochondrial RNA. They have also been shown to increase the activity of several mitochondrial enzymes—notably, alpha-glycerophosphate dehydrogenase, which is important in the metabolism of both fat and carbohydrate.

The thyroid hormones have also been shown to stimulate the incorporation of amino acids into the ribosomes, an effect which depends in vitro on the presence of mitochondria. In vivo, however, there may be in addition a later phase of ribosomal stimulation which is independent of the mitochondria.¹⁶

RELATIONSHIP TO CATECHOLAMINES

T-3 and T-4 enhance the stimulation of lipolysis by adrenaline and noradrenaline, and this may account for part of the calorogenic effect of the thyroid hormones. The calorogenic action of the catecholamines depends on the presence of thyroid hormone. Many of the clinical features of thyrotoxicosis are due to an increased sensitivity of both the cardiovascular and the nervous systems to catecholamines. Because of this the beta-adrenergic blocking agent propranolol has been used for the symptomatic treatment of tachycardia in thyrotoxicosis and in the treatment of thyrotoxic crisis.¹⁷

Laboratory Investigations

Here it is possible to consider only some of the many laboratory investigations which have been used in the clinical assessment of thyroid function. These investigations are of two types: firstly, those which measure thyroid activity; and, secondly, those which help to determine the cause of abnormal function.

The aspects of thyroid function which are measured clinically are iodide trapping (radioiodine uptake), hormone release (PBI and T-3 resin-sponge), and the peripheral response to released hormone (basal metabolic rate). The causes of abnormal function are investigated by tests in which thyroid function is stimulated (TSH), or suppressed (T-3 and perchlorate), and by tests for autoantibodies.

THYROID UPTAKE OF RADIOIODINE

After a tracer amount of iodine-¹³¹ has been given by mouth, the proportion of the dose taken up by the thyroid is measured by a gamma-ray counter placed over the gland. In hyperthyroidism the peak level of uptake is not only greater than in euthyroid people, but occurs earlier. Thus the optimum time for measurement is between two and six hours after giving the isotope. Measurements at 24 hours give better discrimination between the low levels of uptake in hypothyroidism and normal responses.

If radioiodine investigations cannot be avoided in children and pregnant women the radiation dose may be reduced by using ¹²⁵I. The rapid rate of decay of this isotope does not allow late measurements to be made.

The uptake of radioiodine is increased when there is a low level of inorganic iodine in the plasma. On the other hand, a euthyroid person has a reduced uptake when the plasma inorganic iodide level is raised by a large dietary intake of iodine or by the administration of iodine-containing drugs or x-ray contrast media.

¹³¹I is used to determine the activity of thyroid adenomata by scanning, but now technetium-^{99m} is preferred in many centres as it gives results which are at least as good, while the dose of radiation is smaller.¹⁸

SERUM PROTEIN-BOUND IODINE LEVEL

The relation between the serum protein-bound iodine level and the physiological activity of the thyroid hormones in the circulation has been mentioned already. The PBI is affected not only by the level of thyroid activity but also by factors that affect the thyroid hormone-binding proteins and the concentration of iodide in the plasma.

The PBI is lowered in hypoproteinaemia because the levels of the binding proteins are reduced. Oestrogens increase the PBI by increasing the level of TBG, whereas epanutin and salicylate lower the PBI because they compete with T-4 and T-3 for binding sites on TBG. Inorganic iodides—in expectorants, for example—cause spuriously high values unless removed from the serum before the PBI is measured. Organic iodides, in drugs such as Enterovioform (clioquinol) and in x-ray contrast media, raise the PBI level—an effect which lasts a few days after intravenous pyelography and for some years after bronchography and myelography.¹⁹

T₃ RESIN-SPONGE UPTAKE

The in vitro uptake of radioiodine-labelled T-3 by a resin sponge measures the saturation of the thyroid hormone-binding proteins. When a known amount of ¹³¹I-T-3 is added to a standard volume of serum from a patient, the amount of ¹³¹I-T-3 which binds to the serum proteins varies inversely with the amount of endogenous thyroid hormone already bound to protein. Residual free ¹³¹I-T-3 is then absorbed by the sponge, which is removed from the sample before the bound ¹³¹I is measured (Fig. 2.) In hyperthyroidism the saturation of the binding proteins with endogenous T-4 and T-3 is greater than normal; little of the ¹³¹I-T-3 can bind, so that the resin takes up more of the label than normal. In hypothyroidism the proportion of ¹³¹I-T-3 taken up by the resin is reduced. Un-

FIG. 2—In vitro uptake of ¹³¹I-T-3. Partition of isotope between thyroid hormone-binding plasma proteins and resin sponge.

fortunately, the resin uptake is also influenced by the presence of several drugs and hormones.

The results of thyroid hormone release tests are particularly difficult to assess during pregnancy and in women taking oral contraceptives because the high levels of oestrogen in the circulation increase the PBI and reduce the resin-sponge uptake. This difficulty has been overcome by combining the results of both tests to calculate the free thyroxine index and the free thyroxine factor—both of which are independent of binding protein levels.^{20 21}

BASAL METABOLIC RATE

Measuring basal metabolic rate takes more time than the procedures mentioned so far and the patient needs to be prepared with much care. For these reasons and because many factors apart from thyroid activity affect the result this investigation is now used less often than formerly. When performed carefully its accuracy is said to be comparable with that of the other procedures. The basal metabolic rate and other measurements of peripheral response, such as the duration of the Achilles' tendon reflex, are able to show whether a patient being treated with thyroid or antithyroid drugs is euthyroid as the result of treatment.

SUPPRESSION BY TRIIODOTHYRONINE

The cause of a high uptake of radioiodine may be investigated by repeating the procedure after giving triiodothyronine. T-3 does not reduce the overactivity of the thyroid in Graves's disease or suppress autonomous thyroid overactivity. On the other hand, suppression does occur if the gland is normal and in iodine deficiency.

STIMULATION BY TSH

In cases of hypothyroidism secondary to pituitary disease administration of TSH increases the uptake of radioiodine. This test may also be used to show whether the thyroid of a person already being treated with thyroid hormone is capable of functioning.

DISCHARGE OF RADIOIODINE AFTER PERCHLORATE

Rarely hypothyroidism is due to an inherited defect in the production of thyroid hormone. The commonest type of defect affects organification of iodide, so that a short time after a tracer dose of ¹³¹I or ¹²⁵I has been given only a small proportion of the isotope taken up by the gland is bound to protein. Perchlorate interferes with further uptake of radioiodine and the unbound isotope diffuses out. If there is no defect in organification, radioiodine is rapidly bound to protein and is not susceptible to release by perchlorate.

ANTIBODIES

Antibodies to thyroglobulin and to thyroid microsomes are present in high titres in the plasma of nearly all cases of Hashimoto's disease and in other varieties of autoimmune thyroiditis. These antibodies have also been found in the plasma in a large proportion of patients with thyrotoxicosis or with myxoedema.²²

Antibody tests are of value in distinguishing patients with non-toxic goitre from those with Hashimoto's disease, as autoantibodies are absent, or present in low titre, in the former. When hypothyroidism or hyperthyroidism are suspected, high titres suggest autoimmune thyroiditis. High autoantibody titres are a relative contraindication to the surgical treatment of hyperthyroidism because they are associated with an increased risk of postoperative hypothyroidism.²³

Conclusions

Overlap of normal and abnormal ranges frequently makes the results of thyroid investigations difficult to interpret. The results are influenced by many factors that are independent of thyroid activity. Thus thyroid investigations are an invaluable adjunct to clinical judgement but could not be used as an alternative.

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