Int J Endocrinol Metab 2009;7(4): 248-254

REVIEW ARTICLE

Alterations in the Thyroid Axis in Critical Illness: A Brief Review

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Disturbance of the hypothalamo-pituitary-thyroid axis and alteration of circulating thyroid hormones levels are common in non-thyroidal illness (NTI) including infection, burns, and trauma. The commonest abnormality is the low T3 syndrome due to reduced activity of 5′-deiodinase. In acute illness this is associated with an increase in reverse T3 but in more chronic illness reverse T3 is not usually raised. Serum T3 shows a negative correlation with serum concentrations of soluble receptors for TNF and IL-2. Low T3 syndrome may be an appropriate energy-saving adaptation. In critical illness the low T4 syndrome is common. Both total T4 and T3 levels are low. Serum total T4 inversely correlates with mortality. fT4 measurement in critical illness is problematic because of marked method-dependence of results. Direct measurement yields normal/high values but two-step immunoassays used clinically show low values. Falls in the levels of serum thyroid hormone binding proteins and alteration to the affinity of hormone binding due to exogenous and endogenous inhibitors of binding generated in illness further complicate in vivo and in vitro assessment. T4 clearance by deiodination is impaired but non-deiodinative pathways are accelerated. Cellular uptake of free hormone is impaired but expression of nuclear thyroid hormone receptors is increased in critical illness. Serum TSH is normal in the low T3 syndrome but can be low in the low T4 syndrome. Low TSH can be a hypothalamo-pituitary manifestation of illness due to the effect of cytokines on TRH release and TSH synthesis, but TSH is also suppressed by dopamine or glucocorticoid therapy. After drug cessation or in recovery, TSH can transiently increase above the normal range. TSH in critical illness is less glycosylated and less bio-active. Limited trials of T4 and T3 therapy in critical illness have not shown benefit on mortality. No adequate large-scale trial has been conducted.

Key Words: Critical illness, Non-thyroidal illness, Thyroid function

Received: 04.01.2010 **Accepted**: 05.07.2010

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Introduction

Disturbance of the hypothalamo-pituitary-thyroid axis and alteration of circulating thyroid hormones levels are common in non-thyroidal illness (NTI) including infection, burns, trauma, myocardial infarction, and in response to surgery, bone marrow transplantation, and malnutrition, particularly carbohydrate deprivation. In order to understand these pathophysiological processes a brief review of normal thyroid physiology is presented.

Synthesis

Thyroid hormone is synthesized from tyrosine. The 660kD protein thyroglobulin (Tg) functions as a depot prohormone. Iodide is taken up by NIS, the sodium/iodide thyroid membrane symporter, and organified by covalent linkage to the tyrosine residues of

Tg. The two-ring structure of the iodothyronines is created by a coupling reaction of an ether bridge linking two tyrosine rings. Thyroid peroxidase (TPO) is responsible for organification and coupling and is inhibited by the antithyroid thionamide drugs carbimazole and propylthiouracil. TSH stimulates the thyroid at multiple sites including iodide uptake, and hormone synthesis and release.

Circulation

Thyroxine, (T4, 3, 5, 3', 5'-tetraiodothyronine) circulates in greatest concentration (mean total 100nM, free 15 pM, t1/2 7d), compared to the metabolically more active T3(3, 5, 3'-tri-iodothyronine) (total 2 nM, free 4 pM, t1/2 1d), and the calorigenically inactive reverse T3 (rT3, 3, 3', 5'-tri-iodothyronine) (total 0.5nM, t1/2 6h), (Fig. 1).

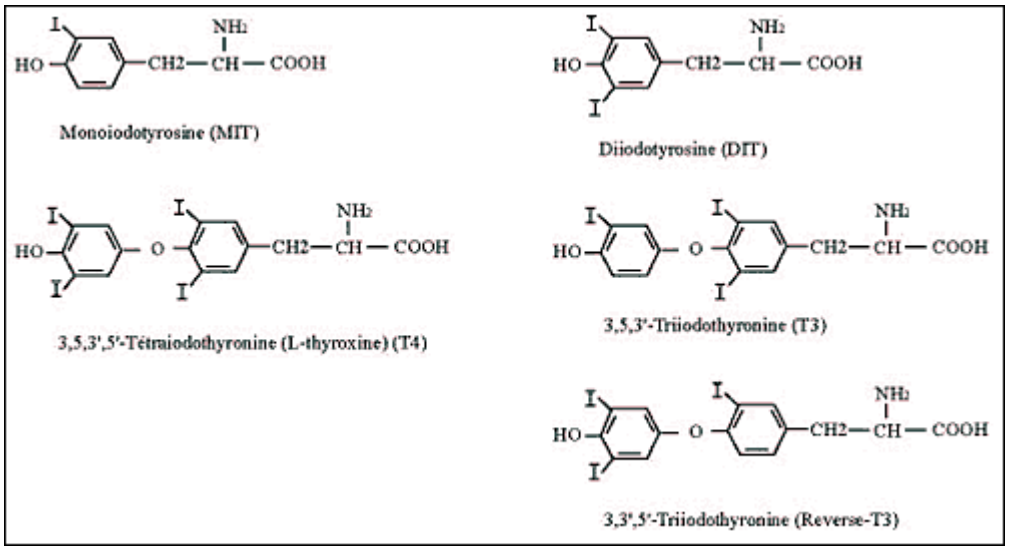

Fig. 1. Structure of iodothyronines (T4, T3 and rT3) and synthetic precursors (MIT and DIT). From Dunn JD. Thyroid Disease Manager, chapter 2. www.thyroidmanager.org

The thyroid gland is the sole source of T4 but the majority of T3 is produced in peripheral tissues by enzymatic cleavage of one outer ring iodine from the T4 molecule. The most active (rapidly equilibrating) sites of deiodination are the liver and kidney, but the (slowly equilibrating) tissues of skin and muscle are also major sites. Thyroid hormone circulates highly bound to plasma proteins: T4 99.97%, T3 99.7%. Thyroxine binding globulin (TBG) is the predominant circulating plasma binding protein: 70% bound T4 (Ka 1010 M-1), 80% bound T3 (Ka 108 M-1), with thyroxine binding prealbumin (transthyretin, TTR) binding 20% of T4 (Ka 106 M-1), and albumin 10% of T4 (Ka 106 M-1). Two thirds of T4 sites on TBG and over 99% of TTR and albumin sites are unoccupied at normal T4 and T3 concentrations. The minute free hormone fraction is in equilibrium with the bound form and is responsible for thyroid hormone action by binding to cellular (nuclear) receptors.

Regulation

Thyroid hormone secretion is regulated by feedback control onto the pituitary by free hormone, which is predominantly circulating T4 deiodinated intracellularly in the pituitary to T3. Only small variations in circulating thyroid hormone levels well within the normal physiological range will serve to augment or inhibit pituitary TSH secretion. Pituitary TSH synthesis and secretion is stimulated by hypothalamic TRH, a cyclic tripeptide which binds to the extracellular domain of a specific G-protein coupled

membrane receptor with seven trans-membrane spanning regions. Signal transduction occurs via the phosphoinositol pathway to generate protein kinase C.

Normal pulsatile TRH secretion is necessary for the correct sialylation of TSH essential for normal bio-activity. TSH is a disulphide-linked two-chain glycoprotein with a specific beta-chain and an alpha-chain common to other glycoproteins (median serum level 1.5 mU/L, t1/2 1h).

Cell transport

Entry of thyroid hormone across the plasma membrane is a specific process but not rate-limiting in normal physiological circumstances. The process is similar to that of L- and T- system amino acid uptake and the OATP (organic anion transport polypeptide) system.

Action

Thyroid hormone acts via a specific nuclear receptor, a 55kD nonhistone nucleoprotein found in the internucleosomal region of DNA with a 10-fold higher affinity for T3 than T4, which is a member of the superfamily of receptors including those for steroid hormones, retinoic acids, vitamin D, and perioxisomal proliferator activating receptors (PPARs). The thyroid hormone receptor has several isoforms. It has DNA and ligand binding domains, and binds to thyroid hormone response elements in the upstream promoter region of responsive genes as a heterodimer with the retinoic acid X receptor. Ligand binding (i.e. T3 binding) relieves gene repression and stimulates gene expression in concert with other nuclear co-repressors and co-activators. Known thyroid hormone responsive genes are the pituitary-expressed TSH and growth hormone genes, myosin heavy chain, sarcoplasmic reticulum calcium-ATPase, and genes involved in lipogenesis such as those for malic enzyme and S14 protein. Thyroid hormone regulates the expression of many genes involved in neurological development in fetal and neonatal life. There is some evidence for non-nuclear receptor-mediated actions of thyroid hormone eg direct mitochondrial actions, but the physiological significance of such putative actions remains to be established.

Metabolism

Thyroid hormone is metabolized in peripheral tissues. T4 to T3 metabolism is activating but otherwise metabolism is to less active or inactive metabolites. In particular inner ring deiodination of T4 to rT3 is an inactivating pathway in which there is progressive deiodination to di-iodo and mono-iodo thyronines. There are non-deiodinative pathways such as sulphation, oxidative deamination, and ether link cleavage (Fig. 2).

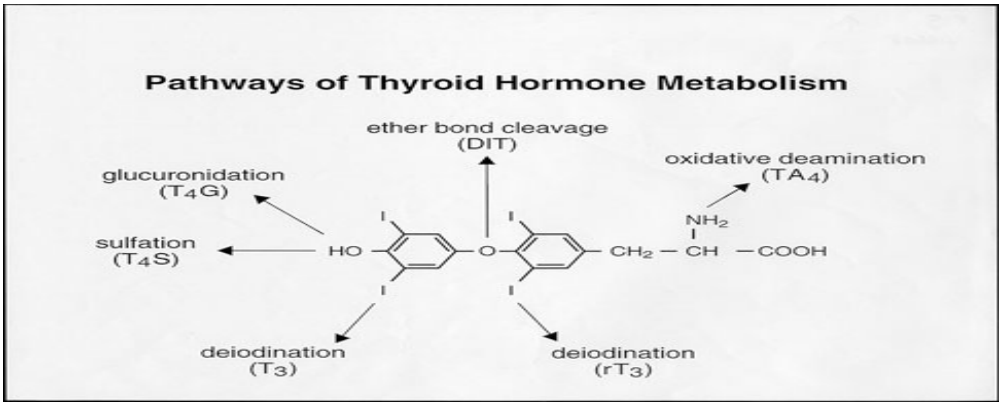

Fig. 2. Thyroid hormone disposal pathways. From Visser TJ.. Thyroid Disease Manager, chapter 3. www.thyroidmanager.org Accessed 13 April 2009

Non-thyroidal illness

The commonest abnormality is the low T3 syndrome in which serum T3 (3, 5, 3' triiodothyronine) falls, mainly due to reduced activity of the 5'-deiodinase type 1 enzyme, resulting in decreased production from thyroxine (T4) usually with an unaltered metabolic clearance rate. The most active sites for this conversion are the liver and kidney (rapidly equilibrating pool) but skin and muscle are also active (slowly equilibrating pool). In acute illness this is often associated with an increase in the metabolically inactive reverse T3 (3, 3', 5' triiodothyronine) but in more chronic illness, e.g. chronic renal failure, reverse T3 is not usually raised. Circulating free T3 concentrations are less affected than total T3 concentrations but methodological issues substantially complicate interpretation of measured free hormone (both fT4 and fT3) levels in critical illness. T3 concentrations show a negative correlation with serum concentrations of soluble receptors for TNF and IL-2. Low T3 syndrome has been teleologically conceived as an appropriate energy saving adaptation.

In critical illness the low T4 syndrome is common in which both total T4 and T3 levels are low. Serum total T4 concentrations inversely correlate with the mortality ratei[1]. The measurement and interpretation of fT4 levels in critical illness continues to be problematic because of marked method-dependence of results[2]. Direct measurement by equilibrium dialysis or ultrafiltration often yields normal or even high values but the two-step immunoassays widely used in clinical chemistry practice show low values. Falls in the absolute levels of serum thyroid hormone binding proteins (albumin, transthyretin and TBG) and alteration to the affinity of hormone binding to these proteins due to exogenous inhibitors of binding (frusemide[3] heparin[4]) and endogenous inhibitors of binding and cellular uptake generated in illness (eg non-esterified fatty acids [NEFA][5], CMPF [3-carboxy-4-methyl-5-propyl-2-furan propanoic acid], indoxyl sulphate[6]) further complicate assessment either by in vivo or in vitro effects. The effect of these inhibitors can be difficult to assess as sample dilution for in vitro hormone assay can obscure the effect of low affinity inhibitors of binding. The free T4 concentration at any time point is a dynamic balance between increased free T4 generation from bound hormone, promoted by endogenous and exogenous inhibitors of binding, and increased clearance of hormone by various pathways. Kinetic analysis in low T4 syndrome shows a drop in T4 production (35%) and in T3 production (83%)[7,8]. Metabolism by deiodination is impaired but non-deiodinative pathways are accelerated. Cellular uptake of free hormone is impaired[9,10] but increased expression of nuclear thyroid hormone receptors in critical illness may act to maintain euthyroidism[11]. Serum TSH is normal in the low T3 syndrome but can be low in the low T4 syndrome. Low TSH can be a hypothalamo-pituitary manifestation of illness due to the effect of cytokines (e.g. IL-6) on TRH stimulation and TSH synthesis and release, but TSH is also suppressed by dopamine infusion[12] or glucocorticoid administration[13]. After cessation of these drugs or in recovery from NTI, TSH can transiently increase above the normal range (to 15-20 mU/L) (Fig. 3) and this may contribute to a rise in circulating T4 towards the normal range[14]. Secreted TSH in critical illness is less sialylated[15] and thus less bioactive than TSH produced in health.

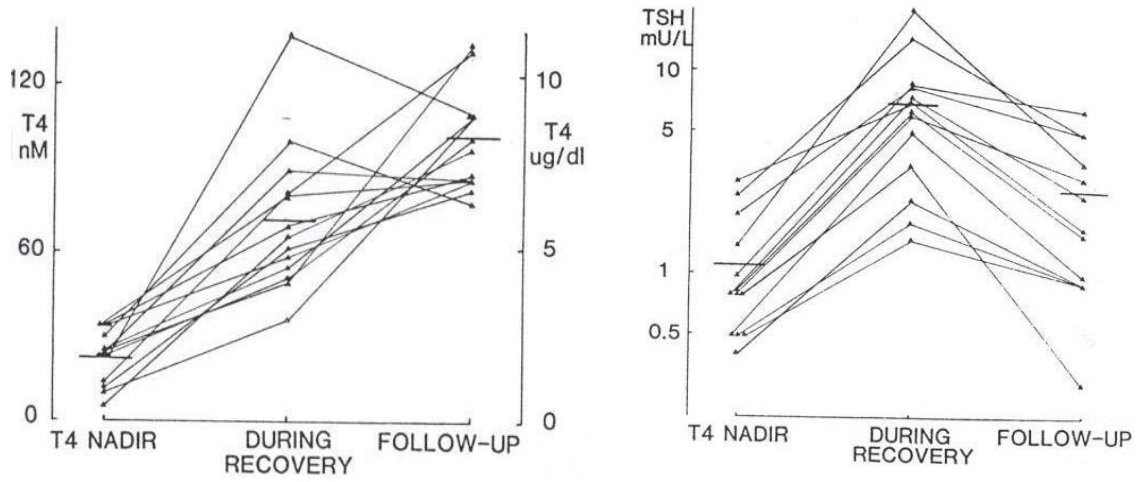

Fig. 3. Recovery from low T4 syndrome: serum total T4 and TSH at nadir of T4, during recovery, and at follow-up. Transient TSH rise during recovery which can be to above normal range. From Hamblin et al, reference 14.

Hyperthyroidism & Hypothyroidism

An important challenge is to diagnose standard forms of thyroid dysfunction in the face of NTI-induced changes in thyroid hormone economy. The effects of the major acute illness and its therapy often substantially compromise clinical assessment. If fT4 and fT3 are elevated and TSH suppressed the diagnosis of hyperthyroidism can generally be made with confidence. NTI can cause normalization of T3 in hyperthyroidism[16], cognate with low T3 syndrome, but the presence of high fT4 and suppressed TSH suggests hyperthyroidism is present. Isolated modest elevation of T4 with normal TSH and normal or low T3 is seen occasionally as an illness or drug effect (eg amiodarone) where T4 clearance is markedly reduced, and does not indicate hyperthyroidism. More challenging is the exclusion of hypothyroidism. If TSH is markedly elevated (> 30 mU/L) at or near the presentation of critical illness this strongly suggests primary hypothyroidism is present but modest TSH elevation up to 15-20mU/L can be seen during recovery from NTI or after cessation of dopamine or glucocorticoid therapy. The differentiation of central forms of hypothyroidism i.e. secondary (pituitary) or tertiary (hypothalamic) hypothyroidism from severe NTI with low T4 and TSH is highly problematic. Conceptually low T4 syndrome may indeed be a form of central hypothyroidism, at least when prolonged, albeit without proof that thyroid hormone therapy is beneficial or even harmless. Practically the retrospective assay of the earliest samples at this hospitalization available for T4 and TSH levels is helpful, as these samples are often normal or much less abnormal, thus indicating that the low hormone levels are of recent origin and thus consistent with NTI, not with already established hypothyroidism (Fig 3 and 4).

Thyroid hormone therapy in NTI

Limited trials of T4 and T3 therapy in critical illness in animal models or in man (Fig. 4) have not shown benefit on mortality[17,18,19]. The suppressive effect of thyroid hormone therapy on TSH may compromise normal recovery from the low T4 syndrome and promote excessive catabolism. No adequate large-scale trial has been conducted[20]. One human model of NTI (low T3 syndrome) is the brain dead organ

donor but the extensive literature on the use of T3 in brain-dead heart donors to improve post-transplant myocardial function although strongly advocated[21] remains inconclusive[22].

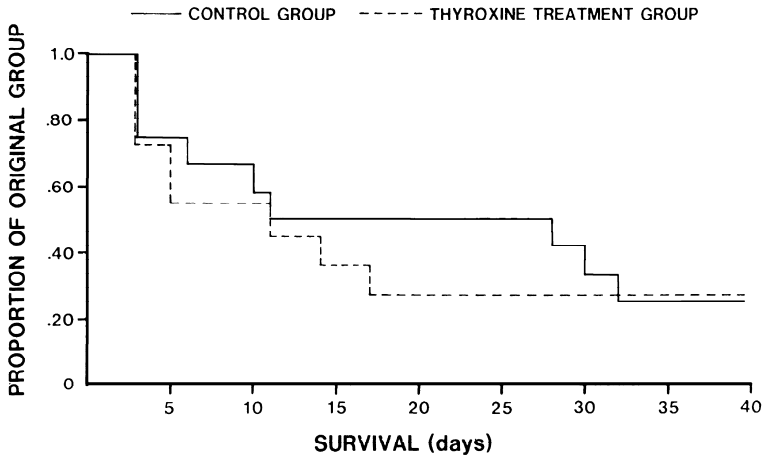

Fig. 4. Kaplan-Meier survival plots in low T4 syndrome critical illness. Patients randomized to T4 therapy or control group. No benefit of T4 therapy evident. From Brent & Hershman, reference 19

Some studies show an apparent benefit but the interpretation of these findings is confounded by suboptimal experimental design and by other interventions such as insulin, glucose, cortisol and vasopressin. Pharmacological T3 therapy appears to function solely as an (expensive) vasodilator[23].

At present thyroid hormone therapy cannot be recommended in critical illness despite alterations in the thyroid axis and abnormal thyroid hormone economy.

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