THYROID HORMONE: SYNTHESIS/SECRETION, FUNCTIONS AND ASSOCIATED DISORDERS AS GROWTH FACTORS

INTRODUCTION

Three main systems of extracellular communication were thought to exist that acted in an integrated fashion helping the organism survive in its environment. These systems are (1) the **immune system** which protects the organism against external and internal perturbances (viruses, bacteria, carcinoma) (2) the **nervous system** whose signals travel by means of electrochemical signals and neurotransmitters between the brain and peripheral tissues and (3) the **endocrine system** which denotes "internal" secretion of substances (hormones) which are released into the circulation by various endocrine glands and act at a site distant from their site of origin. As these systems were studied in detail the distinction between them has blurred. *It is now clear that the nervous system cannot be separated from the endocrine system*. For example, external and internal inputs to the brain alter the expression of hypothalamic releasing inhibitory hormones that are released into the portal capillary system to be delivered to the anterior pituitary. In turn, the pituitary gland, often called the master gland, secretes various hormones that regulate other endocrine organs such as the ***thyroid***, adrenal glands and gonads. Furthermore, certain molecules may act as hormones and neurotransmitters, (e.g. catecholamine). The immune system also interacts with the endocrine system both under physiologic and pathophysiologic conditions. For

example, ***endocrine dysfunction is often autoimmune*** in nature (Hashimoto's hypothyroidism, Graves' hyperthyroidism, type 1 diabetes mellitus). Another example is type 2 diabetes where low-grade systemic inflammation is a major pathophysiologic component.

Hormones are molecules secreted by various endocrine organs and released into the circulation to act at a site distant from their site of origin (**endocrine** fashion). Hormones may also act on the same cell (**autocrine** fashion), or on nearby cells (**paracrine** fashion). Examples include: insulin is secreted by beta islet cells and acts on skeletal muscle to enhance glucose uptake (endocrine), on beta islet cells to inhibit release of insulin (autocrine) and on nearby alpha islet cells to suppress secretion of glucagon (paracrine). The actions of hormones are mediated through binding to specific cellular receptors (membrane, cytoplasmic or nuclear) which have two main properties: **recognition** of the hormone (the ability to distinguish from other molecules) and **signal transduction** (the ability to transmit a message intracellularly).

The physiology of hormonal regulation is beautifully complex and it involves multiple steps: ***synthesis, secretion, transport in the bloodstream, binding to specific receptor and elimination.*** Any of these steps may be affected in disease states.

It is crucial to appreciate that although many major hormones have been identified and characterized, ***new*** hormones ***are being discovered,*** many with important

functions that add to our understanding of endocrine physiology and pathophysiology. Along the way, ***endocrine organs are also being discovered!*** One recent example is the hormone ***leptin*** secreted by the adipose tissue. The discovery of ***leptin*** not only helped us better understand the mechanisms underlying growth and development, sexual function, and food intake but also added the adipose tissue to the endocrine organ family.

FUNCTIONS OF HORMONES

Hormones affect all tissues and organs in the body. Major functions of hormones include:

1. Growth and Development
2. Reproduction
3. Energy metabolism (intake, production, utilization and storage of energy)
4. Maintenance of the internal environment (regulation of blood volume, electrolytes, body temperature, calcium homeostasis etc.)
5. Multiple effects on other organs (skeleton, heart, CNS etc)

There are many ways a hormone can exert its functions:

ONE HORMONE, MANY FUNCTIONS

A single hormone can have different effects at various tissues and some effects may

be present only at certain times of development. For example, ***leptin*** is important in initiating puberty and throughout life for energy regulation. *Excess thyroid hormone may cause hypertrophy of heart muscle,* atrophy of skeletal muscles, and activation of cardiac pacemakers, increases in perspiration, tremor, and menstrual irregularities. The ability of one hormone to exert multiple effects in multiple organs is due to: (1) the ***extensive distribution of hormones*** throughout the body via the circulatory system and (2) the presence of ***different receptors that exhibit differential affinity for the hormone and variable signal transduction properties.***

ONE HORMONE, SPECIFIC FUNCTION

Hormone action can be limited to certain tissues because of: (1) the ***limited distribution of its receptors.*** For example, ACTH secreted by the anterior pituitary, although it circulates freely in the body, only acts on the adrenal glands because only the adrenal cortex has receptors to ACTH. (2) ***Circulation of the hormone in a restricted blood supply.*** For example, CRH is secreted by the hypothalamus into the pituitary venous plexus and acts on the pituitary. Very little CRH can be found circulating in the rest of the body.

ONE FUNCTION, MANY HORMONES

Hormones act in a concerted fashion to maintain normal function of the organism. For example, normal childhood growth, development, and sexual maturation depend on the

proper sequential action of many hormones including *growth hormone, glucocorticoids, thyroid hormone, leptin and sex steroids*. Interruption of any one of these systems will result in a phenotypic abnormality.

CHEMICAL NATURE OF HORMONES

Hormones are derived from other molecules used by the body. Hormones, therefore, can be amino acid derivatives (Thyroxine), modified amino acids (Epinephrine), peptides (ACTH), glycoproteins (Growth Hormone, Luteinizing Hormone), or cholesterol-derived (sex steroids, glucocorticoids, vitamin D). ***In general, protein-derived hormones bind to cell membrane receptors*** that transmit the hormonal signal into the cell while ***cholesterol-derived hormones bind to nuclear receptors*** that interact either directly with the regulatory portions of genes (promoter) or via other transcription factors to alter gene expression. **Exception**: one class of peptide derived hormone, Thyroxine (T4) and Thyronine (T3), whose structure is based on two tyrosine amino acids fused together exert its effects through binding to nuclear receptors.

The thyroid gland produces two related hormones, thyroxine (T4) and triiodothyronine (T3). Acting through thyroid hormone receptors and , these hormones play a critical role in cell differentiation during development and help maintain thermogenic and metabolic homeostasis in the adult. Autoimmune disorders

of the thyroid gland can stimulate overproduction of thyroid hormones (thyrotoxicosis) or cause glandular destruction and hormone deficiency (hypothyroidism).

In addition, benign nodules and various forms of thyroid cancer are relatively common and amenable to detection by physical examination.

ANATOMY

The thyroid (Greek thyreos, shield, plus eidos, form) consists of two lobes connected by an isthmus. It is located anterior to the trachea between the cricoid cartilage and the suprasternal notch. The normal thyroid is 12–20g in size, highly vascular, and so in consistency. Four parathyroid glands, which produce parathyroid hormone, are located posterior to each pole of the thyroid. The recurrent laryngeal nerves traverse the lateral borders of the thyroid gland and must be identified during thyroid surgery to avoid injury and vocal cord paralysis.

DEVELOPMENT

The thyroid gland develops from the floor of the primitive pharynx during the third week of gestation. The developing gland migrates along the thyroglossal duct to reach its final location in the neck. This feature accounts for the rare ectopic location of thyroid tissue at the base of the tongue (lingual thyroid) as well as the occurrence of

thyroglossal duct cysts along this developmental tract. Thyroid hormone synthesis normally begins at about 11 weeks' gestation. Neural crest derivatives from the ultimobranchial body give rise to thyroid medullary C cells that produce calcitonin, a calcium-lowering hormone. The C cells are interspersed throughout the thyroid gland, although their density is greatest in the juncture of the upper one-third and lower two-thirds of the gland. Calcitonin plays a minimal role in calcium homeostasis in humans but the C-cells are important because of their involvement in medullary thyroid cancer.

The thyroid gland consists of numerous spherical follicles composed of thyroid follicular cells that surround secreted colloid, a proteinaceous fluid containing large amounts of thyroglobulin, the protein precursor of thyroid hormones.

REGULATION OF THE THYROID AXIS

SH, secreted by the thyrotrope cells of the anterior pituitary, plays a pivotal role in control of the thyroid axis and serves as the most useful physiologic marker of thyroid hormone action. SH is a 31-kDa hormone composed of and subunits; the subunit is common to the other glycoprotein hormones (luteinizing hormone, follicle -stimulating hormone, human chorionic gonadotropin [HCG]), whereas the SH subunit is unique to SH. The extent and nature of carbohydrate modification are modulated by thyrotropin releasing hormone (RH) stimulation and influences the

biologic activity of the hormone.

The thyroid axis is a classic example of an endocrine feedback loop. Hypothalamic RH stimulates pituitary production of SH, which, in turn, stimulates thyroid hormone synthesis and secretion. Thyroid hormones act via negative feedback predominantly through thyroid hormone receptor 2 (R 2) to inhibit RH and SH production. The "set-point" in this axis is established by SH. RH is the major positive regulator of SH synthesis and secretion. Peak SH secretion occurs ~15 min after administration of exogenous RH.

THYROID HORMONE SYNTHESIS

The thyroid gland is unique among the endocrine glands in its

ability to store its hormone extracellularly and in large quantities. A normal thyroid gland stores enough colloid to provide normal levels of hormone for two to three months. When TSH from the anterior pituitary binds to receptors on follicular cells, their *first* response is to secrete stored thyroid hormone. Their *second* response is to begin synthesizing more colloid to "restock" the follicle lumen. As a general rule,

TSH levels are lower during the day, peak just before sleep, and remain high during the night. Consequently, thyroid hormone release and synthesis follows a similar pattern.

Thyroid hormones are derived from thyroid glands (Tg), a large iodinated glycoprotein. After secretion into the thyroid follicle, Tg is iodinated on tyrosine residues that are subsequently coupled via an ether linkage. Reuptake of Tg into the thyroid follicular cell allows proteolysis and the release of newly synthesized T4 and T3. Iodide uptake is a critical ***first step*** in thyroid hormone synthesis. Ingested iodine is bound to serum proteins, particularly albumin. Unbound iodine is excreted in the urine. The thyroid gland extracts iodine from the circulation in a highly efficient manner. The iodide transport mechanism is highly regulated, allowing adaptation to variations in dietary supply.

Let's examine how follicular cells synthesize thyroid hormone

1. **Thyroglobulin is synthesized and discharged into the follicle lumen.** After being synthesized on the ribosomes of the thyroid's follicular cells, thyroglobulin is transported to the Golgi apparatus, where sugar molecules are attached and the thyroglobulin is packed into transport vesicles. These vesicles move to the apex of the follicular cell, where they discharge their contents into the follicle lumen to become part of the stored colloid.

2. **Iodide is trapped.** To produce the functional iodinated hormones, the follicular cells must accumulate iodides (anions of iodine, I2) from the blood. Iodide trapping depends on active transport. (The concentration of I2 is over 30 times higher inside

the cell than in blood.) Once trapped inside the follicular cell, iodide then moves into the follicle lumen by facilitated diffusion.

3. **Iodide is oxidized to iodine.** At the border of the follicular cell and colloid, iodides are oxidized (by removal of electrons) and converted to iodine (I_2).

4. Iodine is attached to tyrosine. Once formed, iodine is attached to tyrosine amino acids that form part of the thyroglobulin colloid. This iodination reaction, mediated by peroxidase enzymes, occurs at the junction of the follicular cell and the colloid. Attachment of one iodine to a tyrosine produces **monoiodotyrosine** (**MIT**), and attachment of two iodines produces **diiodotyrosine** (**DIT**)

5. **Iodinated tyrosines are linked together to form T3 and T4.**
Enzymes in the colloid link MIT and DIT together. Two linked DITs result in T4, and coupling of MIT and DIT produces T3. At this point, the hormones are still part of the thyroglobulin colloid.

6. **Thyroglobulin colloid is endocytosed.** To secrete the hormones, the follicular cells must reclaim iodinated thyroglobulin by endocytosis and combine the vesicles with lysosomes.

7. **Lysosomal enzymes cleave T4 and T3 from thyroglobulin and the hormones diffuse from the follicular cell into the bloodstream.** The main hormonal product secreted is

T4. Some T4 is converted to T3 before secretion, but most T3 is generated in the peripheral tissues.

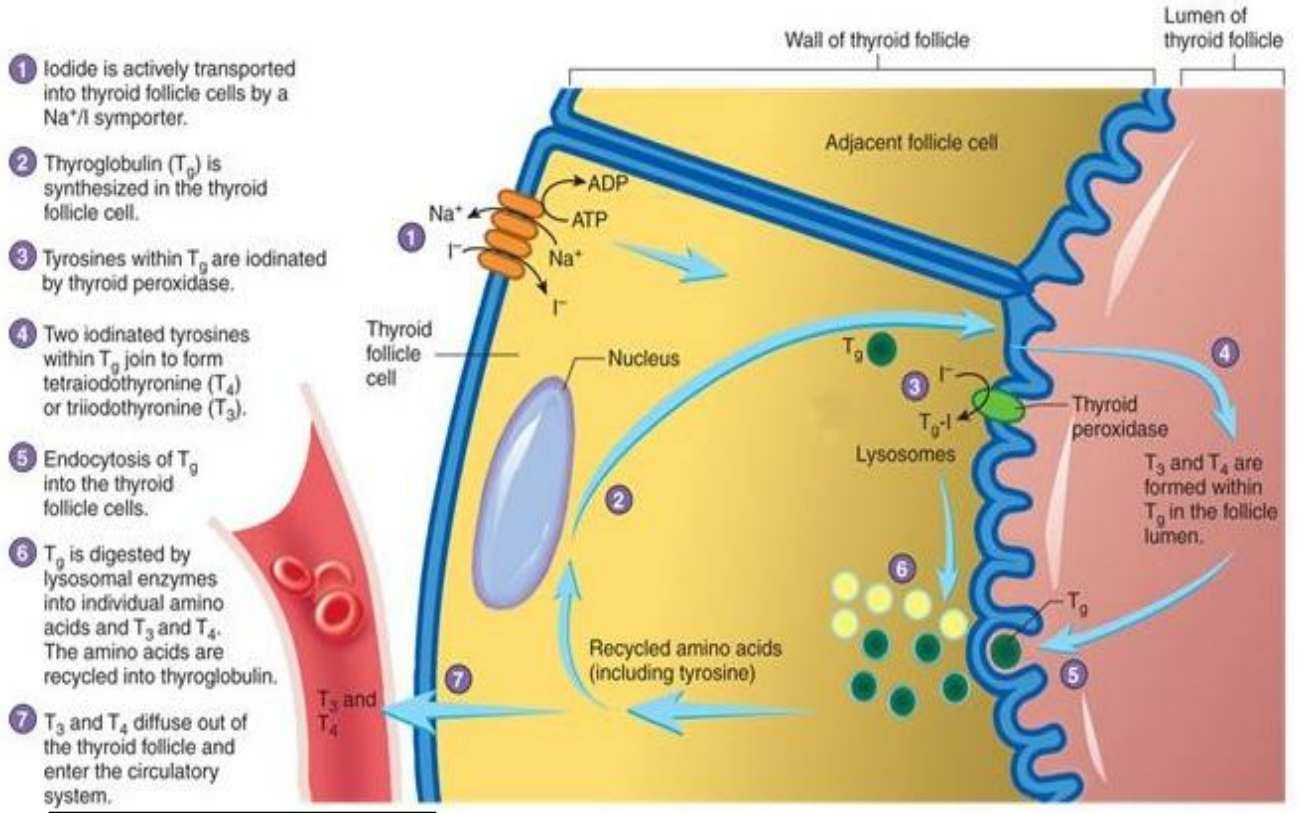

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Fig. 1: *Thyroid hormone secretion*

TSH ACTION

SH regulates thyroid gland unction through the SH-R, a seven-transmembrane G protein–coupled receptor (GPCR). The SH-R is coupled to the subunit of stimulatory G protein (GS), which activates adenylyl cyclase, leading to increased production of

cyclic adenosine monophosphate (AMP). SH also stimulates phosphatidylinositol turnover by activating phospholipase C. The functional role of the SH-R is exemplified by the consequences of naturally occurring mutations.

OTHER FACTORS THAT INFLUENCE HORMONE SYNTHESIS AND RELEASE

Although SH is the dominant hormonal regulator of thyroid gland growth and function, a variety of growth actors, most produced locally in the thyroid gland, also influence thyroid hormone synthesis. These include insulin-like growth factor I (IGF-I), epidermal growth factor, transforming growth factor (GF-), endothelins, and various cytokines. The quantitative roles of these actors are not well understood, but they are important in selected disease states. In acromegaly, for example, increased levels of growth hormone and IGF-I are associated with goiter and predisposition to multi-nodular goiter (MNG). Certain cytokines and interleukins (ILs) produced in association with autoimmune thyroid disease induce thyroid growth, whereas others lead to apoptosis. Iodine deficiency increases thyroid blood flow and regulates the NIS stimulating more efficient iodine uptake. Excess iodide transiently inhibits thyroid iodide organification, a phenomenon known as the ***Wol - Chaiko effect.*** In individuals with a normal thyroid, the gland escapes from this inhibitory effect and iodide organification resumes; the suppressive action of high iodide may persist, however, in patients with underlying autoimmune thyroid disease.

THYROID HORMONE TRANSPORT AND METABOLISM

T4 is secreted from the thyroid gland in about twenty old excess over T3. Both hormones are bound to plasma proteins, including thyroxine-binding globulin (BG), transthyretin (R, formerly known as thyroxine-binding pre-albumin, or BPA), and albumin. The plasma-binding proteins increase the pool of circulating hormone, delay hormone clearance, and may modulate hormone delivery to selected tissue sites. The concentration of BG is relatively low (1–2 mg/dL), but because of its high affinity for thyroid hormones (T4 >T3), it carries about 80% of the bound hormones. Albumin has relatively low affinity for thyroid hormones but has a high plasma concentration (~3.5 g/dL), and it binds up to 10% of T4 and 30% of T3. R carries about 10% of T4 but little T3. When the effects of the various binding proteins are combined, approximately 99.98% of T4 and 99.7% of T3 are protein-bound. Because T3 is less tightly bound than T4, the fraction of unbound T3 is greater than unbound T4, but there is less unbound T3 in the circulation because it is produced in smaller amounts and cleared more rapidly than T4. The unbound or "free" concentrations of the hormones are ~2 × 10-11 M for T4 and ~6× 10-12 M for T3, which roughly correspond to the thyroid hormone receptor binding constants or these hormones. The unbound hormone is thought to be biologically available to tissues. Nonetheless, the homeostatic mechanisms that regulate the thyroid axis are directed toward maintenance of normal

concentrations of unbound hormones.

THYROID HORMONE ACTION

(Thyroid hormone transport)

Circulating thyroid hormones enter cells by passive diffusion and via specific transporters such as the monocarboxylate 8 transporter (MC 8), MC 10, and organic anion-transporting polypeptide 1C1. Mutations in the MC 8 gene have been identified in patients with X-linked psychomotor retardation and thyroid function abnormalities (low T4, high T3, and high SH). After entering cells, thyroid hormones act primarily through nuclear receptors, although they also have nongenomic actions through stimulating mitochondrial enzymatic responses and may act directly on blood vessels and the heart through integrin receptors.

NUCLEAR THYROID HORMONE RECEPTORS

Thyroid hormones bind with high affinity to nuclear thyroid hormone receptors (Rs) and . Both R and R are expressed in most tissues, but their relative expression levels vary among organs; R is particularly abundant in brain, kidneys, gonads, muscle, and heart, whereas R expression is relatively high in the pituitary and liver. Both receptors are variably spliced to form unique isoforms. The R 2 isoform, which has a unique amino terminus, is selectively expressed in the hypothalamus and pituitary, where it plays a role in feedback control of the thyroid axis. The R 2 isoform contains a unique carboxyl terminus that precludes thyroid hormone binding;

it may function to block the action of other R isoforms. The Rs contain a central DNA -binding domain and a C-terminal ligand-binding domain. They bind to specific DNA sequences, termed ***thyroid response elements*** (TREs), in the promoter regions of target genes. The receptors bind as homodimers or, more commonly, as heterodimers with retinoic acid X receptors (RXRs). The activated receptor can either stimulate gene transcription (e.g., myosin heavy chain) or inhibit transcription (e.g., SH -subunit gene), depending on the nature of the regulatory elements in the target gene. Thyroid hormones (T3 and T4) bind with similar affinities to R and R . However, structural differences in the ligand binding domains provide the potential or developing receptor -selective agonists or antagonists, and these are under investigation. T3 is bound with 10–15 times greater affinity than 4, which explains its increased hormonal potency.

THYROID HORMONE RESISTANCE

Resistance to thyroid hormone (RTH) is an autosomal dominant disorder characterized by elevated thyroid hormone levels and inappropriately normal or elevated SH. Individuals with R H do not, in general, exhibit signs and symptoms that are typical of hypothyroidism.

The histopathology varies with the etiology and duration of the goiter. Initially, there is a uniform hyperplasia but as the disorder persists, the thyroid architecture loses its uniformity with development of areas of involution or fibrosis interspersed with areas of focal hyperplasia resulting in multiple nodules and the formation of a multinodular goiter (MNG). Many diffusely enlarged goiters are composed of multiple soft nodules which cannot be palpated individually. Accumulation of colloid may also contribute to the nodularity of the goiter. Hemorrhage or cystic degeneration of a hyperplastic nodule can result in a sudden focal increase in size of a goiter. In areas of growth, regression and hemorrhage, irregular calcifications can occur. The evolution of this multinodular stage is accompanied by the development of "hot" (hyperfunctioning) and "cold" (non-functional) nodules on thyroid nuclear scan (Technicium 99m pertechnetate or I-123 radioiodine) with functional autonomy.

THYROID HORMONE RECEPTOR EXPRESSION

Data in this area of research is sketchy and there are not enough actual results to elaborate on the true condition of thyroid hormone expression. Experimental study on animal model emphasizes that thyroid hormone receptor expression during sickness and starvation positively correlated with its reduction. In one study the non-thyroidal illness was inducted on animal model which was followed by thyroid hormone receptor metabolic dysfunction (Rodriguez-Perez et al., 2008; D'Amati et al., 2001;

Sanchez and Jolin, 1991; Mansourian, 2011a).

Correlation of non-thyroidal illness and hypothyroid manifestation: Various studies indicated that although during non-thyroidal illness there is a reduction of thyroid hormones (http://www.scialert.net/asci/result.php?searchin=Keywords&cat=&ascicat=ALL&Submit=Search&keyword=thyroid+hormones) particularly serum T3, but the hypothyroid index is not obvious but patients clinically manifest some degree of hypothyroidism. The hypothyroid clinical manifestation such as febrile, edema, sepsis, sedative, cardio pulmonary abnormalities usually are accompanied with thyroid hormones (http://www.scialert.net/asci/result.php?searchin=Keywords&cat=&ascicat=ALL&Submit=Search&keyword=thyroid+hormones) disorders of non-thyroidal illness. Although clinical manifestation of hypothyroidism are not visible in the initial state of non-thyroidal illness but it can be manifested in later stage of disease onset I profile alteration, liver enzymes activity modification, basic metabolic rate changes are not clearly giving any documented clue to the presentation of hypothyroid state during non-thyroidal illness. Also some variation in some biochemical indices such as angiotensin converting enzyme, anti-thrombin, were seen in some experimental studies on animal models with inducted non-thyroidal illness and T3 administration can return some of those modification to reference standards, but the demonstration of hypothyroidism during non-thyroidal illness is not presented as clinical symptom

(Brent et al., 1984; Seppel et al., 1996; Plikat et al., 2007).

Metabolic pathways behind serum thyroxin and triidothyronine alteration level during non-thyroidal illness: There is not a single reason for non-thyroidal illness and there are many reasons that can be conducted into non-thyroidal diseases in spite that the original cause of illness is not similar in every person. It should be mentioned that the liver and kidney dysfunctions demonstrate different form of clinical manifestation compared to other types of non-thyroidal diseases. As example the disorders in hypothalamus-pituitary physiological functions reduce the biosynthesis of TSH with subsequent suppression of total T4, leading to reduction of serum T3 concentration. In a experimental study on animal model with non-thyroidal illness which caused by starvation accompanied by reduced T4 and leptin the biosynthesis of TRH from hypothalamus is induced by leptin an stimulator of hypothalamus which was followed by the elevation of serum T4 reaching to reference range of normal. In another experimental study which non-thyroidal illness was carried out on rat by inducing starvation the nuclear mechanism of TRH production is reduced with subsequent adverse effect on TSH biosynthesis. The reduced production of TSH leads to reduced T4 and ultimately T3 reduction (Blake et al., 1991; Fliers et al., 1997; Vierhapper et al., 1982; Faber et al., 1987; Mansourian, 2012a).

Clinical studies indicated that TRH prescription can be a vital inducer in correcting the serum T4 with subsequent elevation of T3 level through enhanced serum TSH

concentration as result of TRH administration in patients suffering from non-thyroidal illness. This later statement can be a crucial suggestion in the role of suppressed hypothalamus physiological function in causing non thyroidal illness (Van den Berghe et al., 1998a; Nicolow et al.,1970).

Studies indicated that elevated concentration of cortisol in adrenal cortex dysfunction can cause a reduction in the amount of TSH with subsequent suppression in the amount of thyroid hormone level. There are documented reports indicating elevated amount of cortisol and in general glucocorticoids can be an important barrier in pituitary for TRH to act on and produce TSH, as result of suppressed TSH, thyroid hormones (http://www.scialert.net/asci/result.php?searching=Keywords&cat=&ascicat=ALL&Submit=Search&keyword=thyroid+hormones) of T4, T3 are reduced as well (Brabant et al., 1987; Benker et al., 1990; Bianco et al., 1987). Any stress stimulation in animal leading to elevated concentration of glucocorticoids causing suppression of TSH as result of diminished TRH with T4,T3 reduction eventually (Bianco et al., 1987). This is the explanation behind suppressed biosynthesis of TSH in pituitary in spite of low T4, T3. It seems that the pituitary intracellular conversion of T4 into T3 can be as reason for pituitary to remain at euthyroid clinical condition, but it is not true for the rest of human organs and they are in practice exhibit hypothyroid condition, although other study proved otherwise. Although there are other possibilities such as thyroxin by

product for the above physiological function related to pituitary reaction during non thyroidal illness was presented, but there is not proper explanation in that why the pituitary alone should be in the euthyroid but other tissues in hypothyroid status (Lim et al., 1984; Mebis et al.,

2006). The scientific explanation which are acceptable in this area of research come from the fact that hypothalamus stimulation which can be occurred through many inducing factors such as ***starvation, stress, cortisol and glucocorticoids*** in general and cytokines are behind reasons for the pituitary to behave in manner explained above. The cortisol which can be secreted during stress can be a suppressing factor for pituitary to retard the production of TSH, in fact as result of depleted TRH which coming from hypothalamus. The other adverse side effect in the latest scenario, is the reduction of Luteinizing Hormone (LH) and Follicle Stimulating Hormone (FSH), which are pituitary hormones also suppressed during non-thyroidal illness leading to reduction in the sex hormones mainly testosterone. All these changes most possibly originated from hypothalamus neuron modification as result some physiological changes such as stress, starvation, cytokines and glucocorticoids happen during serious illness. In some cases all these physiological alteration eventually lead to thyroid hormones (http://www.scialert.net/asci/result.php?searchin=Keywords&cat=&ascicat=ALL&Submit=Search&keyword=thyroid+hormones) suppression with eventual hypothyroidism.

Selenium is an element behave as Co-factor in the structure of iodothyronine deiodinase enzyme and selenium deficiency eventually lead to deiodinase dysfunction. This later enzyme is responsible for T3 production from T4 reverse T3 (rT3) retardation and mainly is found within liver (Kaplan, 1979). Some studies indicated that the reason for low T3 is not based on T4 slow cellular penetration and if it was the case the level of T4 should have been increased instead of suppression. Focusing on this later manifestation some are in believe that there is a possibility that the activity of deiodinase enzyme responsible for T4 conversion to T3 is diminished due selenium deficiency which is playing the co-factor role for the deiodinase and on the absence of such element the enzyme is not able to convert the T4 into T3 and therefore T4 concentration is increased while T3 is reduced, although there is controversy in this area as well (Van den Berghe et al., 1998b). During non-thyroidal illness T4, T3 catabolizing pathways is significantly decreased as the concentration of T4, T3 are reduced simultaneously. Some are in believe that the diminished thyroid hormones (http://www.scialert.net/asci/result.php?

searchin=Keywords&cat=&ascicat=ALL&Submit=Search&keyword=thyroid+hormones) destruction can initially elevate the thyroid hormones concentrations and not the down-grading of thyroid hormones (http://www.scialert.net/asci/result.php? searchin=Keywords&cat=&ascicat=ALL&Submit=Search&keyword=thyroid+hormones) degradation. It should be mentioned that reduced degradation of thyroid hormones

(http://www.scialert.net/asci/result.php?searchin=Keywords&cat=&ascicat=ALL&Submit=Search&keyword=thyroid+hormones) are as result of lower available thyroid hormones(http://www.scialert.net/asci/result.php?searchin=Keywords&cat=&ascicat=LL&Submit=Search&keyword=thyroid+hormones). Other study emphasize on the role of lower inactive form of Thyroxin Binding Globulin (TBG) during some critical illness (Afandi et al., 2000).

As human arrive into short period of starvation and some other stress during critical diseases, the reduced concentration of T3 which in part is to diminished activity of deiodinase and retardation of T4 into T3 is a natural response to limit the basic metabolic rate and prevent energy loss and keep it for a forcible future during the sever diseases. Later in the course of illness the suppression of thyroid hormones (http://www.scialert.net/asci/result.php?searchin=Keywords&cat=&ascicat=ALL&Submit=Search&keyword=thyroid+hormones) and some other pituitary hormones and in fact many other metabolic alterations are clinically manifested which in fact are the physiological consequence of non-thyroidal illness. The pathophysiological response during non-thyroidal illness is accompanied with insulin level abnormality, negative nitrogen balance, lipid accumulation on condition the supply of energy provided from some other sources. There are variety of other dysfunctions in the course of illness, neuron and heart disorders are among them. Studies in this field of research suggesting hormone-substituting replacement therapy in those hormones such as

thyroid, growth and androgen hormones should be carried out to prevent the adverse effect of illness (Mebis et al., 2006; Van den Berghe et al., 1998b, 2001; Weekers et al., 2003; Mansourian, 2010d, e, 2011c, Mansourian et al., 2007, 2008; Mansourian, 2010).

Some studies indicated that in non-thyroidal illness such as sepsis it was shown that T4, T3 and TSH are reduced while interleukins are increased. It seems that glucocorticoids level is increased, but TSH concentration is reduced and further studies is demonstrated that interlukines can be preventive factor in the production of TSH, with ultimate T4, T3 reduction (Monig et al., 1999; Hermus et al., 1992).

As the dosage of some interleukins increased some clinical manifestation such as febrile, inadequate food intake (http://www.scialert.net/asci/result.php?searchin=Keywords&cat=&ascicat=ALL&Submit=Search&keyword=food+intake) are observed which can play a role in the reduction of thyroid hormone as natural consequences of non-thyroidal illness. Some interleukins showed to be a causative factor in the thyroid hormones (http://www.scialert.net/asci/result.php?searchin=Keywords&cat=&ascicat=ALL&Submit=Search&keyword=thyroid+hormones) biosynthesis in thyroid gland and this become even worse in various diseases originated from non thyroidal illness, but the role of interleukins in other studies have been contradicted. The interventional mechanism of cytokines in hypothalamus-pituitary axis is not fully understood but it

most probable involved with disturbing of TRH-TSH axis and reducing TSH leading to reduction in thyroid hormones (http://www.scialert.net/asci/result.php?searchin=Keywords&cat=&ascicat=ALL&Submit=Search&keyword=thyroid+hormones). Although the cytokines are manufactured by various dysfunctions such as various infections, inflammations, neoplastic illness. In spite all controversial which are existed in this area of no thyroidal illness, cytokines involvement during non-thyroidal illness eventually lead to thyroid hormones (http://www.scialert.net/asci/result.php?searchin=Keywords&cat=&ascicat=ALL&Submit=Search&keyword=thyroid+hormones) dysfunctions (Cannon et al., 1990; Van der Poll et al., 1990, 1995, 1999; De Metz et al., 2000; Chopra et al., 1991; Nagaya et al., 2000; Bartalena et al., 1994; Boelen et al., 1993, 1995, 1996, 1997; Abozenah et al., 2008; Stouthard et al., 1994; De Metz et al., 2000; Michalaki et al., 2001).

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