Functional Medicine University's Functional Diagnostic Medicine Training Program

Module 7 * FMDT 563A

Physiology of the Thyroid Gland

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The spectrum of the clinical presentation of thyroid dysfunction ranges from subclinical asymptomatic to an overt thyroid storm. Therefore, it is important to recognize signs and symptoms, *as well as* the physical examination presentation.

TABLE 10.3 — SYMPTOMS AND SIGNS OF HYPOTHYROID AND HYPERTHYROID

Hypothyroid		Hyperthyroid	
Symptoms	**Signs**	**Symptoms**	**Signs**
Fatigue	Pale, dry skin	Palpitations	Fast heart rate
Weakness	Coarse, dry hair	Heat intolerance	Trembling hands
Weight gain or increased difficulty losing weight	A puffy face	Nervousness	Weight loss
Hair loss	Hoarse voice	Insomnia	Muscle weakness
Cold intolerance	Elevated blood cholesterol level	Breathlessness	Warm, moist skin
Muscle cramps		Increased bowel movements	Hair loss
Constipation		Light or absent menstrual periods	Staring gaze
Depression		Fatigue	
Irritability			
Memory loss			
Abnormal menstruation			
Decreased libido			

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Manifestations of Hyperthyroidism

General	Fatigue, heat intolerance, sweating, weight loss,
Dermatological	Pruritus, warm moist skin
Ophthalmologic	Ophthalmopathy (eyelid lag or retraction, exophthalmoses) of Graves' disease
Neck	Goiter
Pulmonary	Dyspnea, tachypnea, signs of pulmonary hypertension
Cardiac	Palpitations, tachycardia, atrial fibrillation, high-output cardiac state
Gastrointestinal	Increased stool frequency
Genitourinary	Menstrual disorders, infertility
Neuromuscular	Muscular weakness, fine tremor, hyperreflexia
Psychiatric	Anxiety, nervousness

Manifestations of Hypothyroidism

General	Fatigue, weight gain, anemia, cold intolerance
Dermatologic	Dry course skin, brittle hair, hair loss, non-pitting edema
Ears, Eyes, Throat	Hearing loss, hoarse voice, periorbital edema, facial puffiness
Neck	Goiter
Pulmonary	Dyspnea, pleural effusions, hypoventilation, sleep apnea
Cardiac	Bradycardia, congestive heart failure, pericardial effusions
Gastrointestinal	Anorexia, constipation
Genitourinary	Menstrual disorders, decreased libido, impotence, infertility
Neuromuscular	Muscle weakness, delayed ankle jerk relaxation phase
Psychiatric	Depression, psychomotor retardation, coma

Anatomically, the thyroid gland is located just below the larynx on both sides of the trachea. The physical examination should consist of both inspection and palpation. A normal thyroid in the adult is estimated to be 10 to 20 grams in weight. The gland should be inspected anteriorly and laterally. Cross-lighting increases shadows and can improve the detection of masses. Palpation can be performed from the anterior or posterior approach.

Posterior Approach of Thyroid Palpation

1. The patient is examined in the seated or standing position
2. Standing behind the patient, attempt to locate the thyroid isthmus by palpating between the cricoid cartilage and the suprasternal notch
3. Move your hands laterally to try to feel under the SCMs for the fullness of the thyroid
4. Have the patient swallow a sip of water as you palpate, feeling for the upward movement of the thyroid gland.

Note: Normally, the gland should be barely palpable.

Physiologic Effects of Thyroid Hormones

It is likely that all cells in the body are targets for thyroid hormones. Thyroid hormones have profound effects on many physiologic processes, such as *development*, *growth*, and *metabolism.* Thyroid hormones stimulate diverse metabolic activities in most tissues, leading to an increase in basal metabolic rate. One consequence of this activity is to increase body heat production, which seems to result, at least in part, from increased oxygen consumption and rates of ATP hydrolysis.

- *Lipid metabolism*: Increased thyroid hormone levels stimulate fat mobilization, leading to increased concentrations of fatty acids in plasma. They also enhance oxidation of fatty acids in many tissues. Finally, plasma concentrations of cholesterol and triglycerides are inversely correlated with thyroid hormone levels – one diagnostic indication of hypothyroidism is increased blood cholesterol concentration.

- *Carbohydrate metabolism*: Thyroid hormones stimulate almost all aspects of carbohydrate metabolism, including enhancement of insulin-dependent entry of glucose into cells and increased gluconeogenesis and glycogenolysis to generate free glucose.

Growth: Thyroid hormones are clearly necessary for normal growth in children, as evidenced by the growth-retardation observed in thyroid deficiency. The growth-promoting effect of thyroid hormones is intimately intertwined with that of growth hormone, a clear indication that complex physiologic processes like growth depend upon multiple endocrine controls.

Development: Of critical importance in mammals is the fact that normal levels of thyroid hormone are essential to the development of the fetal and neonatal brain.

- *Cardiovascular system*: Thyroid hormones increase heart rate, cardiac contractility and cardiac output. They also promote vasodilation, which leads to enhanced blood flow to many organs.

- *Central nervous system*: Both decreased and increased concentrations of thyroid hormones lead to alterations in mental state. Too little thyroid hormone will tend to cause sluggishness, while too much induces anxiety and nervousness.

- *Reproductive system:* Normal reproductive behavior and physiology is dependent on having essentially normal levels of thyroid hormone. Hypothyroidism, in particular, is commonly associated with infertility.

Thyroid Hormones

The thyroid secretes three hormones:

1. Thyroxine (T4)
2. Triiodothyronine (T3)
3. Calcitonin - this hormone is involved with calcium metabolism

Synthesis and Secretion of Thyroid Hormones

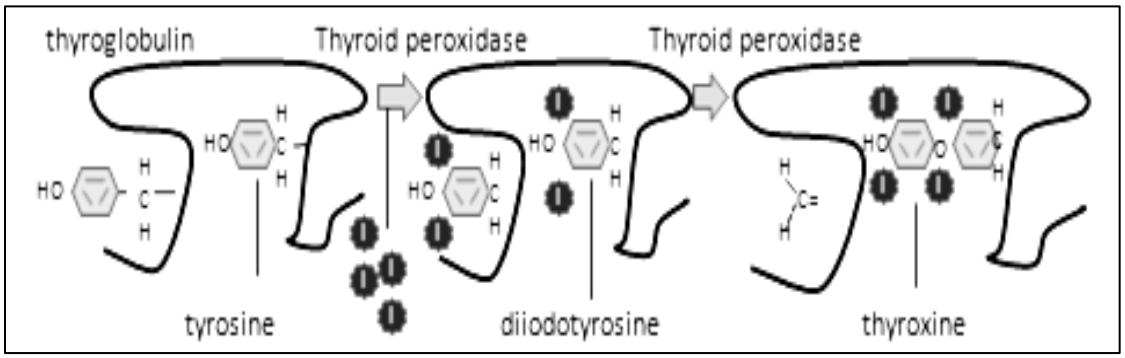
Thyroid hormones are synthesized by mechanisms fundamentally different from what is seen in other endocrine systems. Thyroid follicles serve as both factory and warehouse for production of thyroid hormones. About 93% of the secretion of thyroid hormones from the thyroid gland is T4, with about 7% being T3. It's important to keep in mind that most of T4 is converted to T3 in the periphery. The functions of these two hormones are qualitatively the same but differ in the rapidity and intensity of action. Triiodothyronine is about four times as potent as thyroxine, but it is present in the blood in much smaller quantities and persists for a much shorter time than does thyroxine.[2]

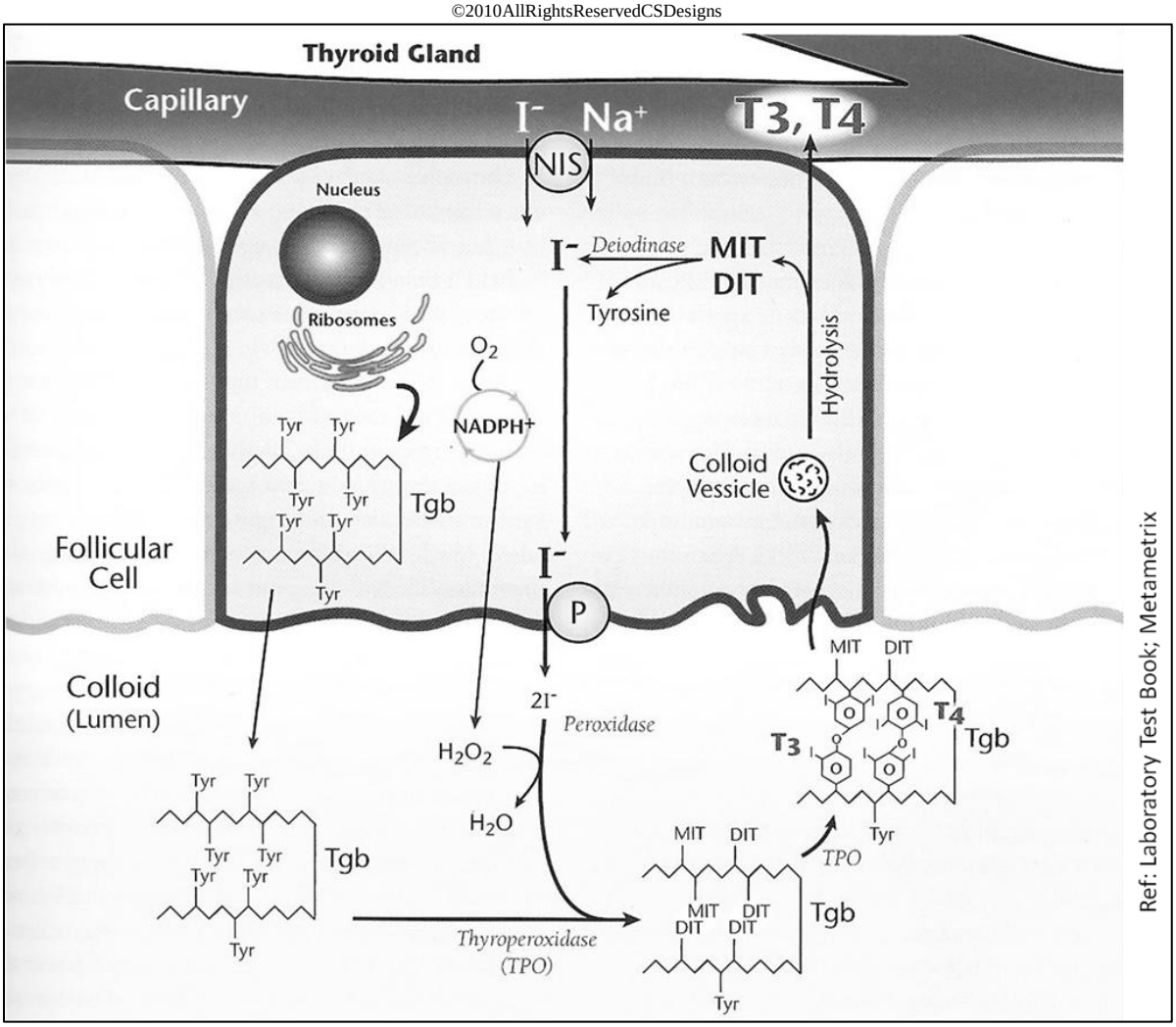
The synthesis occurs in three major steps.

1. Accumulation of raw materials
    - Tyrosines *are provided from a large glycoprotein scaffold called thyroglobulin, which is synthesized by thyroid epithelial cells and secreted into the lumen of the follicle-colloid which is essentially a pool of thyroglobulin.*
    - Iodine*, or more accurately iodide (I^-), is avidly taken up from blood by thyroid epithelial cells, which have on their outer plasma membrane a sodium-iodine symporter or 'iodine trap'. Once inside the cell, iodide is transported into the lumen of the follicle along with thyroglobulin.*
2. Fabrication or synthesis of the hormones on a backbone or scaffold of precursor
3. Release of the free hormones from the scaffold and secretion into blood

Fabrication of thyroid hormones is conducted by the enzyme thyroid peroxidase, an integral membrane protein present in the apical (colloid-facing) plasma membrane of thyroid epithelial cells. Thyroid peroxidase catalyzes two sequential reactions:

- Iodination of tyrosines on thyroglobulin (also known as 'organification of iodide')
- Synthesis of thyroxine or triiodothyronine from two iodotyrosines





Through the action of thyroid peroxidase, thyroid hormones accumulate in colloid on the surface of thyroid epithelial cells. Remember that hormone is still tied up in molecules of thyroglobulin – the remaining task is to liberate it from the scaffold and secrete free hormone into blood.

Thyroid hormones are excised from their thyroglobulin scaffold by digestion in lysosomes of thyroid epithelial cells. This final act in thyroid hormone synthesis proceeds in the following steps:

- Thyroid epithelial cells ingest colloid by endocytosis from their apical borders- colloid contains thyroglobulin decorated with thyroid hormone.
- Colloid-laden endosomes fuse with lysosomes, which contain hydrolytic enzymes that digest thyroglobulin, thereby liberating free thyroid hormones.
- Finally, free thyroid hormones diffuse out of lysosomes, through the basal plasma membrane of the cell, and into blood where they quickly bind to carrier proteins for transport to target cells.

The Sodium-Iodide Symporter

The ability of the thyroid gland to transport and concentrate iodine from blood is absolutely necessary for the synthesis of thyroid hormones. The key player in this process is the sodium-iodine symporter, an integral membrane protein that resides in the basolateral membrane of thyroid epithelial cells.

Considering critical role of iodine trapping in the thyroid function, it is not surprising that abnormalities in expression or function of the symporter can lead to thyroid disease. Two such situations have been identified in humans.

- Inactivating mutations in the symporter gene result in congenital hypothyroidism. In several patients with this disorder, specific missense mutations in the symporter mRNA have been characterized.
- Autoantibodies to the symporter protein adversely affect iodide transport. A substantial number of patients with autoimmune (Hashimoto's) thyroiditis have anti-symporter antibodies, and application of these antibodies to cultured cells expressing the symporter inhibits iodide uptake.

The sodium-iodide symporter cannot distinguish between normal and radioactive iodide, thus providing a useful exploit for diagnosis and treatment of certain thyroid disease. Small amounts of radioactive iodine injected into patients are rapidly concentrated in the thyroid, providing a means to image the thyroid for detection of tumors and other abnormalities. Administration of higher doses of radioiodine is widely used for treatment of hyperthyroidism and some types of thyroid cancer; in this case the radioactivity is concentrated rather precisely in the tissue requiring destruction. As functional medicine practitioners, we are interested in healing the gland by addressing all aspects of immune dysfunction.

Chemistry of Thyroid Hormones

T4

- Is synthesized from the amino acid tyrosine and iodine, is produced in the thyroid in response to TSH, and is converted into either T3 or Reverse T3 (rT3) in the peripheral tissue.

- Is either stored in the follicle of gland or released from thyroid into the blood stream primarily bound to thyroid binding globulin.

- Deficiencies of zinc, copper, and vitamins A, B2, B3, B6, and C will cause a decrease in production of T4 by the follicles of the thyroid gland.

- Only about 0.03 – 0.05% of circulating T4 is in a free form. The rest is bound to thyroid binding globulin, albumin, and thyroid-binding prealbumin.

- Is either converted to T3 or rT3, or eliminated via conjugation, deamination or decarboxylation in the liver. It is estimated that about 70% of T4 produced in the thyroid is eventually deiodinated in peripheral tissues into either T3 or rT3 via the deiodinase enzyme that cleaves an iodine molecule from the quaternary form.

- Total T4 reflects the total amount of T4 present in the blood i.e. amount bound to thyroid binding globulin and free levels.

T3

- Is considered the most metabolically active thyroid hormone, is 4-5 times more metabolically active that T4, and its systemic effects and half-life are shorter. Although some is produced in the thyroid, approximately 80-85% is produced outside the thyroid, primarily by conversion of T4 in the liver and kidneys. Within the liver and kidney, the enzyme responsible for the peripheral conversion of T4 is a selenium dependent enzyme called 5'-deiodinase.

- Similar to T4, the majority of T3 is in a protein bound form. Total T3 reflects the total amount of T3 present in the blood i.e. amount bound to protein and free levels. Free T3 represents approximately 8-10% of circulating T3. Free T3 is more available for tissue receptors and provides a more accurate measurement for thyroid assessment in the presence of factors that affects binding proteins.

Reverse T3

- T4 can also be converted into a molecule of reverse T3 (rT3) in the peripheral tissues. 95% of rT3 is produced from peripheral conversion of T4. The enzyme responsible for this conversion is 5-deiodinase and is not believed to be dependent on selenium.

Reverse T3 (con't)

- Under normal conditions, 45-50% of the daily production of T4 is transformed into rT3. Reverse T3 can be seen as a sort of 'blocker molecule' that fits in and occupies the T3 receptors in the target cells.

- The production of rT3 is also subject to a range of environmental, lifestyle, and physiological influences. Adrenal stress levels have a major influence on the production of rT3.

Transport of Thyroid Hormones

Thyroid hormones are poorly soluble in water, and most of the T3 and T4 circulating in blood is bound to carrier proteins. After leaving the thyroid gland, over 99 percent of T4 and T3 are immediately combined with several proteins in the plasma. The principle carrier of thyroid hormones is *thyroid-binding globulin*, a glycoprotein synthesized in the liver. Two other carriers of importance are transthyrein and albumin. Carrier proteins allow maintenance of a stable pool of thyroid hormones from which the active, free hormones are released for uptake by target cells.

Thyroid-Binding Globulin

TBG is the major thyroid hormone protein carrier. It is primarily produced in the liver and is affected by liver dysfunction. Laboratory testing is used in the evaluation of patients who have abnormal total T4 and T3 levels. When performed concurrently with a T4/T3 test, the T4 and T3 levels can be more easily interpreted.

Test Explanation

Assays of T4 and T3 are a measure of total T4/T3 levels. That is, they are a measure of bound and unbound thyroid hormones. Most of these hormones are bound to TBG. The unbound or 'free T4/T3' is the metabolically active hormone. Certain illnesses are associated with elevated or decreased TBG levels. With increased TBG levels, more T4 and T3 are bound to that protein. Less free, metabolically active T4/T3 is available. TSH is stimulated to produce higher levels of T4 and T3 to compensate. T4 and T3 levels increase but do not cause hyperthyroidism because the increase is merely a compensation for the increased TBG. When total T4 is elevated, one must ascertain whether that elevation is due to an elevation in TBG or a real elevation in T4 alone associated with hyperthyroidism.

The most common causes of elevated TBG are pregnancy, hormone replacement therapy, or use of oral contraceptives. Elevated TBG is also present in some cases of porphyria and in infectious hepatitis. Decreased TBG is commonly associated with other causes of hypoproteinemia (e.g., nephrotic syndrome, gastrointestinal (GI) malabsorption, malnutrition).

Interfering Factors of Thyroid-Binding Globulin (TBG)

- Drugs that *increase* TBG include:
  - Estrogens
  - Methadone
  - Tamoxifen
  - Oral contraceptives
- Drugs that *decrease* TBG include:
  - Steroids
  - Androgens
  - Danazol
  - Phenytoin (Dilantin)
  - Propanolol

Effect of Thyroid Hormone

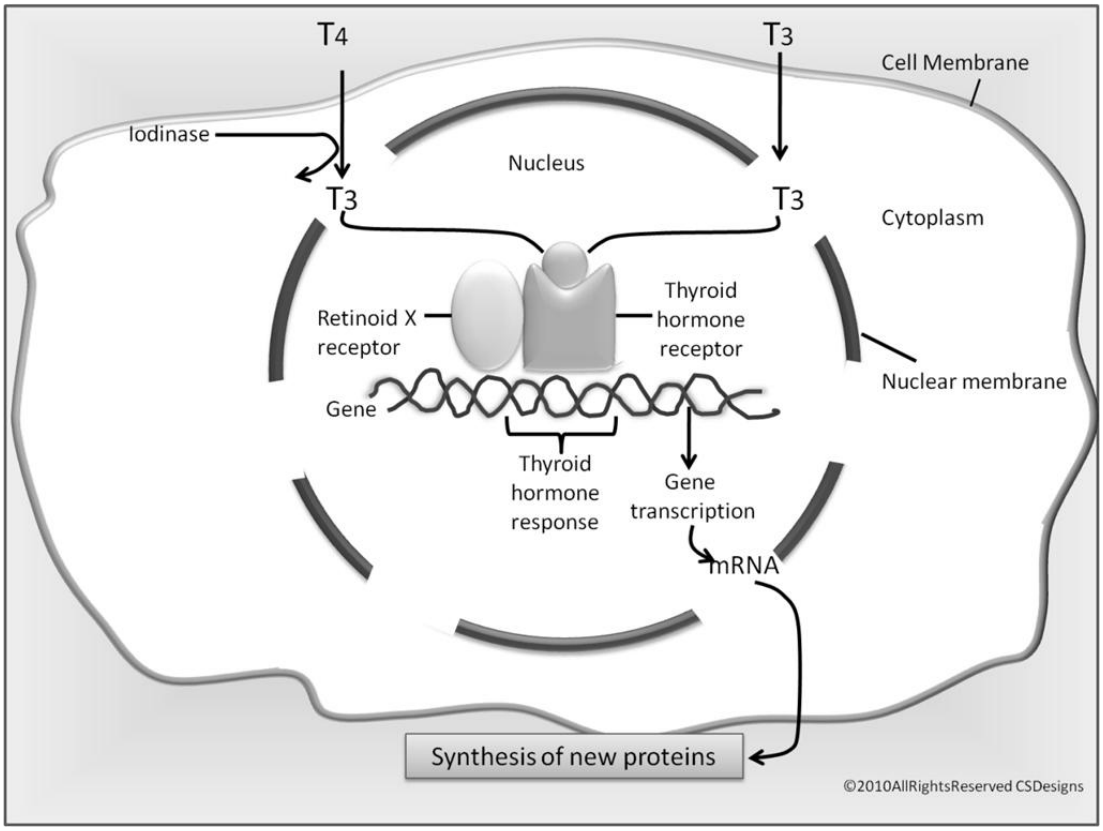
The main effect of thyroid hormone is to activate nuclear transcription, which in turn, causes protein synthesis. Thyroid hormone also causes other metabolic functions.

- Increases cellular metabolic activity by increasing the number and activity of mitochondria, as well as increasing active transport of the cell membranes.
- Promote growth and development
- Stimulates carbohydrate metabolism
- Stimulates fat metabolism
- Has an effect on plasma and liver fats
- Increases basal metabolic rate
- Decreases body weight
- Has an effect on the cardiovascular system – increase of blood flow, cardiac output, heart rate, heart strength
- Increases respiration
- Increases gastrointestinal motility
- Excitatory effect on the central nervous system
- Increases the rate of secretion of most all other endocrine glands
- Has an effect on sexual function

Thyroid Hormone Receptors and Nuclear Transcription

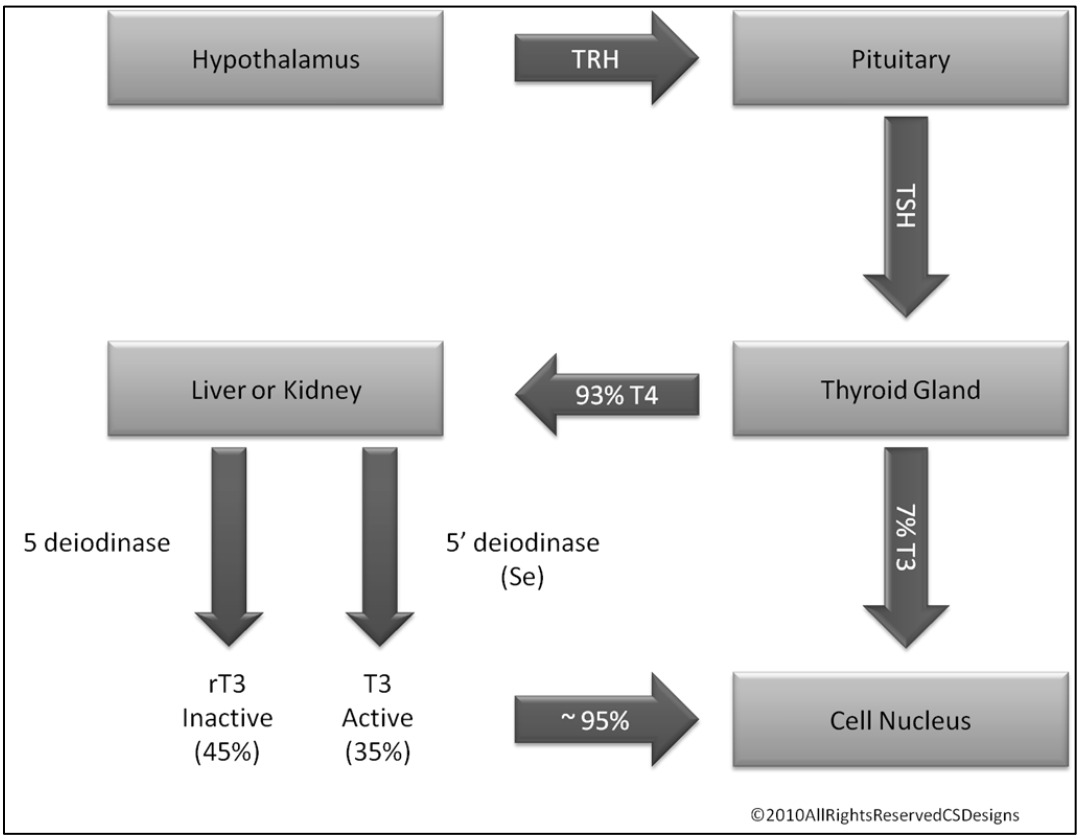
The steroid and thyroid hormone superfamily of receptors are proteins that are bi-functional, capable of binding hormone as well as directly activating gene transcription. Because these receptors bind ligand intracellularly and then interact with DNA directly they are more commonly called the nuclear receptors.

Unlike peptide hormone receptors, that spans the plasma membrane and bind ligand outside the cell, steroid hormone receptors are found in the cytosol and the nucleus. The steroid hormone receptors belong to the steroid and thyroid hormone receptor super-family of proteins, that includes not only the receptors for steroid hormones (androgen receptor, AR; progesterone receptor PR; estrogen receptor, ER), but also for thyroid hormone (TR), vitamin D (VDR), retinoic acid (RAR), mineralocorticoids (MR), and glucocorticoids (GR).



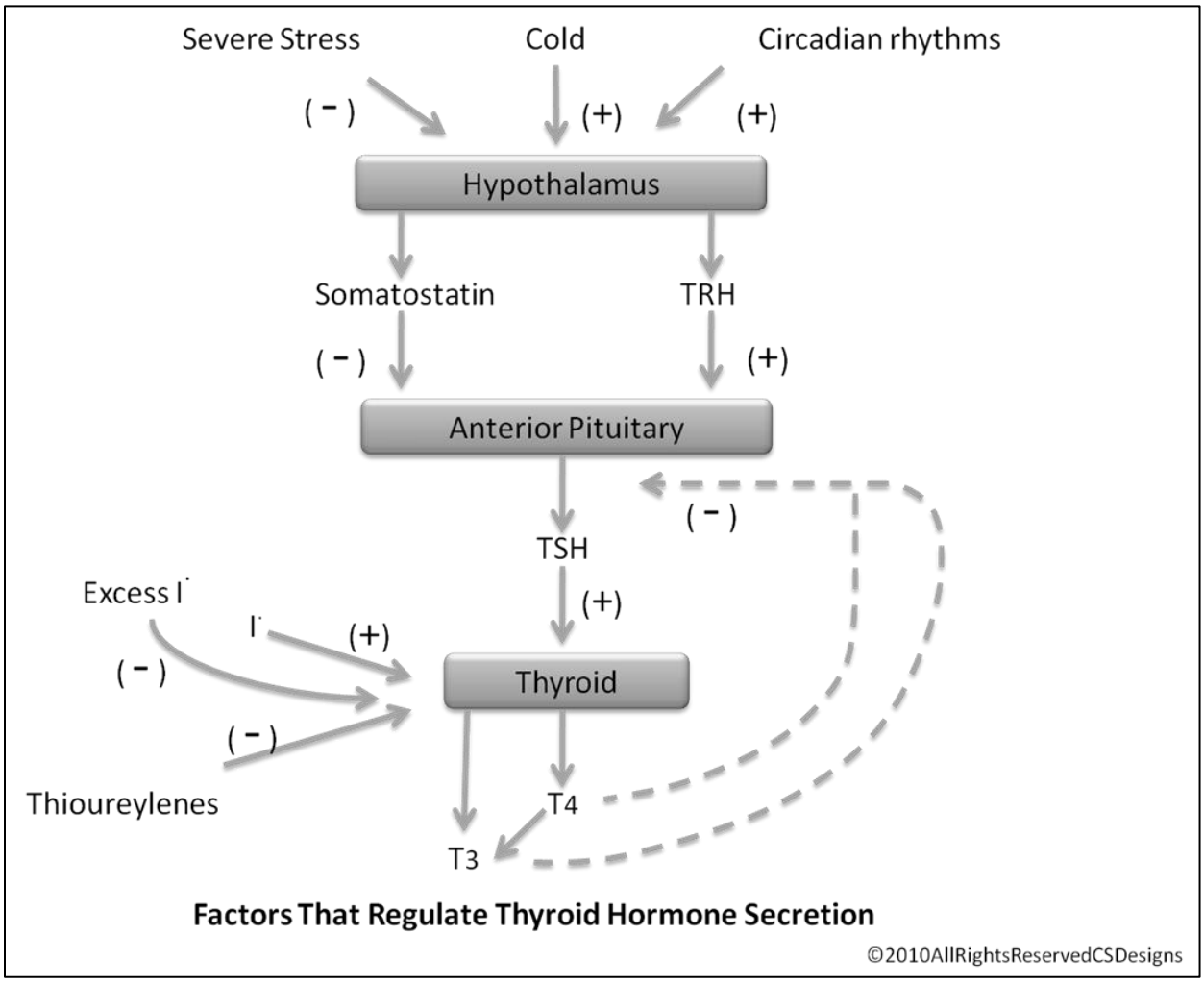
Thyroid receptors are either attached to the DNA genetic strands or located in proximity to them. The thyroid hormone receptor usually forms a heterodimer (a protein made of two different subunits) with retinoid X receptor (RXR) at specific thyroid receptor response elements on the DNA. Thyroid hormone enters the target cell by facilitative diffusion. Thyroid hormone interacts with a heterodimer receptor (thyroid hormone receptor and retinoid X receptor). The combination of the heterodimer and thyroid hormone activates the thyroid hormone response gene.

Retinoic acid is a metabolite of vitamin A binds to several heterodimers, one of which is retinoid X receptor. Retinoids influence cell growth and differentiation through retinoid receptors, retinoic acid and retinoid X receptor. It is interesting to note that clinical and in vitro studies suggest that some patients with advanced thyroid cancer may respond to therapy with retinoic acid. Research has indicated that vitamin A, as well as Vitamin D, can regulate gene expression, due to the fact that they share similar pathways with thyroid hormone. Elevated homocysteine can inhibit retinoic acid synthesis, which in turn can affect receptor activity.



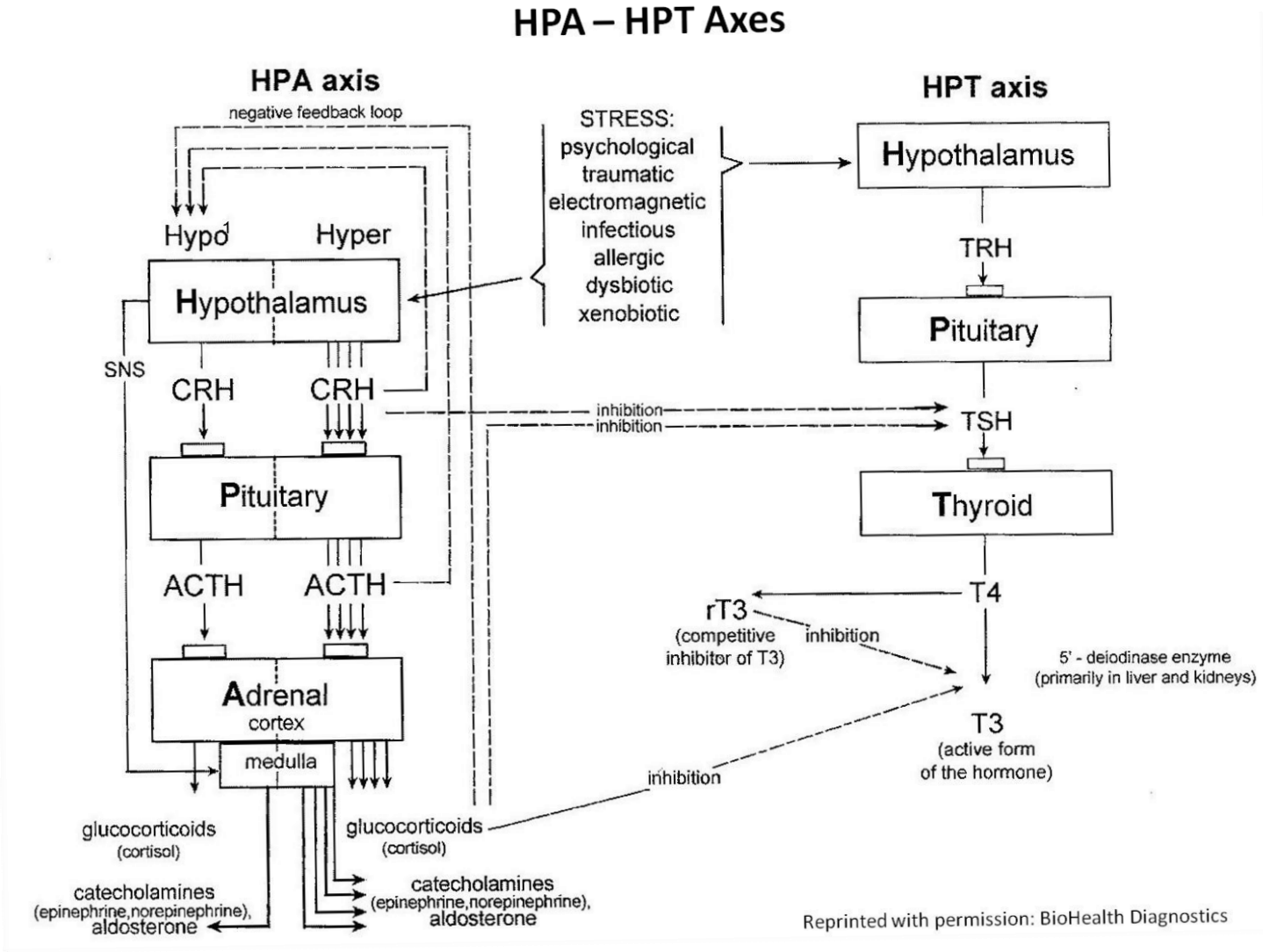
Control of Thyroid Hormone Synthesis and Secretion

The chief stimulator of thyroid hormone synthesis is thyroid-stimulating hormone from the anterior pituitary. Binding of TSH to receptors on thyroid epithelial cells enhances all of the processes necessary for synthesis of thyroid hormone, including synthesis of the iodide transporter, thyroid peroxidase, and thyroglobulin. The magnitude of the TSH signal also sets the rate of endocytosis of colloid – high concentrations of TSH lead to faster rates of endocytosis, and hence, thyroid hormone release into the circulation. Conversely, when TSH levels are low, rates of thyroid hormone synthesis and release diminish.



Feedback effect of Thyroid Hormone

As thyroid hormone increases in the body fluids, a decrease in secretion of TSH from the anterior pituitary ensues. Increased thyroid hormone seems to mainly affect the anterior pituitary's secretion of TSH.


HPA – HPT Axes
HPA axis
negative feedback loop
Hypo
Hyper
Hypothalamus
SNS
CRH
CRH
Pituitary
ACTH
ACTH
Adrenal
cortex
medulla
glucocorticoids
(cortisol)
catecholamines
(epinephrine,norepinephrine),
aldosterone
STRESS:
psychological
traumatic
electromagnetic
infectious
allergic
dysbiotic
xenobiotic
glucocorticoids
(cortisol)
catecholamines
(epinephrine,norepinephrine),
aldosterone
HPT axis
Hypothalamus
TRH
Pituitary
inhibition
inhibition
TSH
Thyroid
T4
rT3
(competitive
inhibitor of T3)
inhibition
5' - deiodinase enzyme
(primarily in liver and kidneys)
T3
(active form
of the hormone)
inhibition
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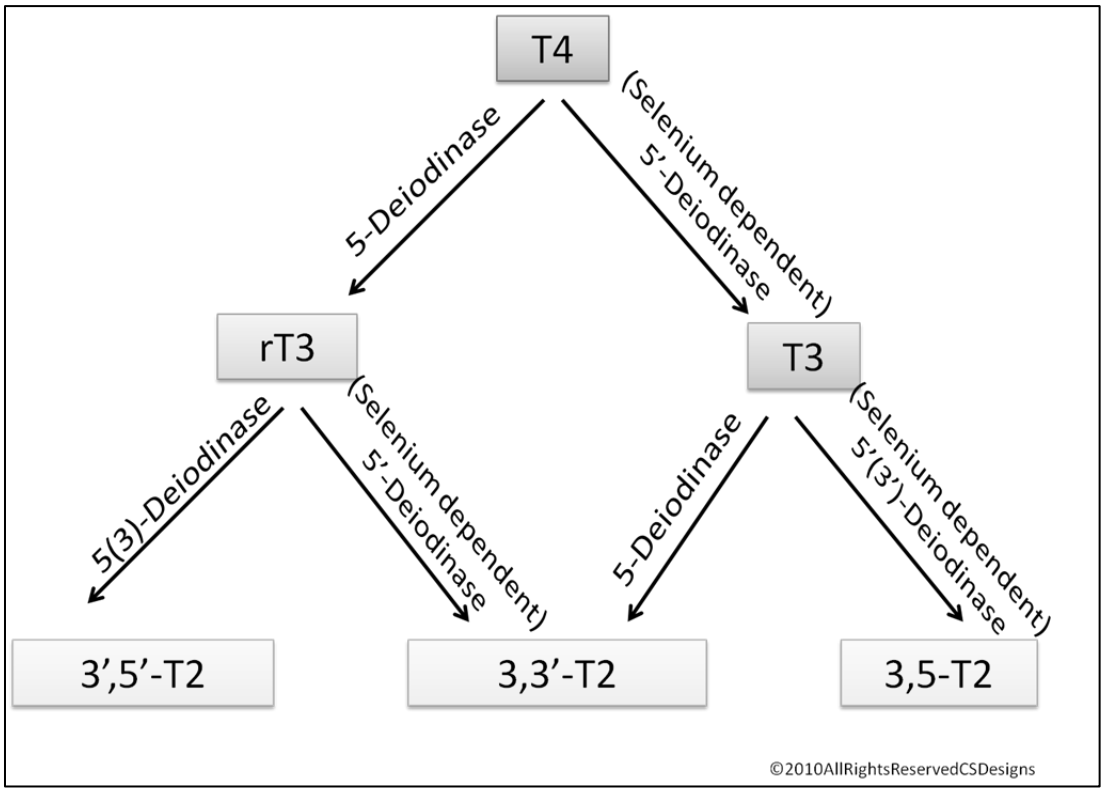
Peripheral Conversion of T4 to T3

Physiological responses to circulating T4 depend upon its peripheral conversion to T3 by enzymes that require selenium. Patients with normal circulating of TSH and T4 who display clinical hypothyroid symptoms may be selenium depleted. The enzyme responsible for the conversion of T4 to T3 is called 5'-deiodinase.



Selenium

- Is an essential nutrient for 5' – deiodinase activity, the enzyme involved in the peripheral conversion of T4 and T3.
- Also necessary to degrade rT3
- Adequacy Assessment:
  - RBC, whole blood, hair, serum, urine (TSH, TT_4, TT_3)
- Optimal forms: Mixed selenocompounds including: selenocysteine, selenomethionine, se-methylselenocysteine
- Clinical indications of deficiency:
  - Compromised immunity, male & female reproductive health, cardiovascular health, inflammation regulation in asthma and thyroid hormone metabolism.
  - Low selenium levels are associated with diminished deiodination of T4 and T3.
  - Consider deficiency if Total T3 is reduced and/or T3 is reduced with a normal TSH and T4 level
- Food Sources: garlic, onions, broccoli, brazil nuts, brewer's yeast
- Occupies a unique position regarding biochemical and physiological mechanisms
- Selenium can replace the sulfur atom in cysteine, creating a selenocysteine residue.
- Selenocysteine (selenoprotein) is the 21st acid recognized as part of the universal genetic code.

Selenoproteins

- Glutathione peroxidase (GPx)
  - Reduction of ROS (hydrogen peroxide)
  - Protection from oxidation stress
- Thioredoxin reductase (TR)
  - Reduces Vitamin C, lipoic acid, coenzyme Q10, Vitamin K
- A selenium-deficient state may lead to uncontrolled release of metals, especially copper and cadmium, contributing to toxicity.

Selenium & The Thyroid Gland

- Normal functioning thyroid gland is dependent upon the selenoprotein iodothyronine deiodinase (ID).
- ID converts T_4 (thyroxin) to the metabolically active T_3 (triiodothyronine).
- Supplementation with selenium in patients with autoimmune thyroiditis has been shown to significantly reduce antibody production and oxidative stress.

Clinical Association of Selenium

- Selenium deficiency affects most physiological systems
  - Endocrine
  - Immunological
  - Gastrointestinal
  - Musculoskeletal
  - Key nutrient in cancer prevention and treatment
- Individuals with elevated body burden of toxic elements have greater difficulty maintaining sufficient selenium levels.

Selenium toxicity (Selenosis)

- Rare (usually by contaminated soil)
- Signs & Symptoms
  - Garlic breath
  - Thick, brittle fingernails
  - Dry brittle hair
  - Red swollen hands & feet
  - Numbness, convulsions, paralysis

Assessment of Selenium Status

- Narrow therapeutic window. Evaluation is essential for determining the need for therapy.
- Functional marker
  - Serum T_4 elevated with depressed T_3

(peripheral conversion of T_4 to T_3 is a selenium dependant enzyme called 5'deiodinase. Iodine is removed from the 5' site on the first Tyrosyl residual)

Selenium - reference ranges

- Serum
  - 95-165 ng/mL
  - 40% higher in whole blood
  - Critical values: >500 ng/mL
- Urinary – 24 hr
  - Selenometabolites are excreted in the urine
    - e.g. monomethylselenium & selenosugars
  - Reference ranges: 15-150 ug/L
- RBC selenium
  - If low selenium – selenium deficiency
  - If normal – may not represent normal levels (may still be deficient)
- Hair – selenium
  - Hair concentrations correlate with those of blood
  - May accurately reflect status
  - Rule out exogenous selenium (shampoos)

Selenium Repletion

- Best absorbed form is selenomethionine
- Se-methylselenocysteine is less toxic
- RDA 55 ug/day
- Repletion dose 60-100 ug/day

Summary

A basic and advanced understanding of thyroid hormone synthesis, secretion and effect is imperative to implementing an effective treatment plan. A later lesson in this module will provide a detailed functional medicine treatment approach to managing thyroid dysfunction.

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