LDN and Thyroid Disorders

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LDN and Thyroid Disorders

- Autoimmune thyroiditis
  - Hashimoto's
    - Antithyroglobulin
    - Anti-TPO AB
  - Grave's disease
    - Thyroid stimulating immunoglobulin

LDN and Thyroid Disorders

- Hashimoto’s generally described as TH1 dominant and Grave’s as TH2
- Significant individual variation
- Can be either TH1 or TH2 dominant
- LDN can potentially be useful for both

Phenikos C, et al. Th1 and Th2 serum cytokine profiles characterize patients with Hashimoto's thyroiditis (Th1) and Graves' disease (Th2). Neuroimmunomodulation. 2004;11(4):209-13.

Nanba, et al. Increases of the Th1/Th2 cell ratio in severe Hashimoto's disease and in the proportion of Th17 cells in intractable Graves' disease. Thyroid. 2009 May;19(5):495-501

LDN and Thyroid Disorders

- Hashimoto's and Graves often associated with or initiated or driven by chronic infections or gut dysbiosis. Also, modern diet plays a role with food allergies or sensitivities (gluten) or driven by ingestion of trans- fatty acids and/or GMO.
- Different intestinal bacteria can stimulate differing Th1/TH2 responses
  - Streptococcus thermophilus, lactobacillus bulgaris and B. bifidum, which are widely used in the making of commercial yogurt, stimulate Th2
- Toxic metals
- Hormones
- Estrogen, progesterone and cortisol generally decrease TH1/TH2 ratio (conflicting data)
- Testosterone generally increase Th1/TH2 ratio

Marin ML, Tejada-Simon MV, Lee, JH. Stimulation of cytokine production in clonal macrophage and T-cell models by Streptococcus thermophilus: comparison with Bifidobacterium sp. and Lactobacillus bulgaricusJ Food Prot 1998 Jul;61(7):859-64

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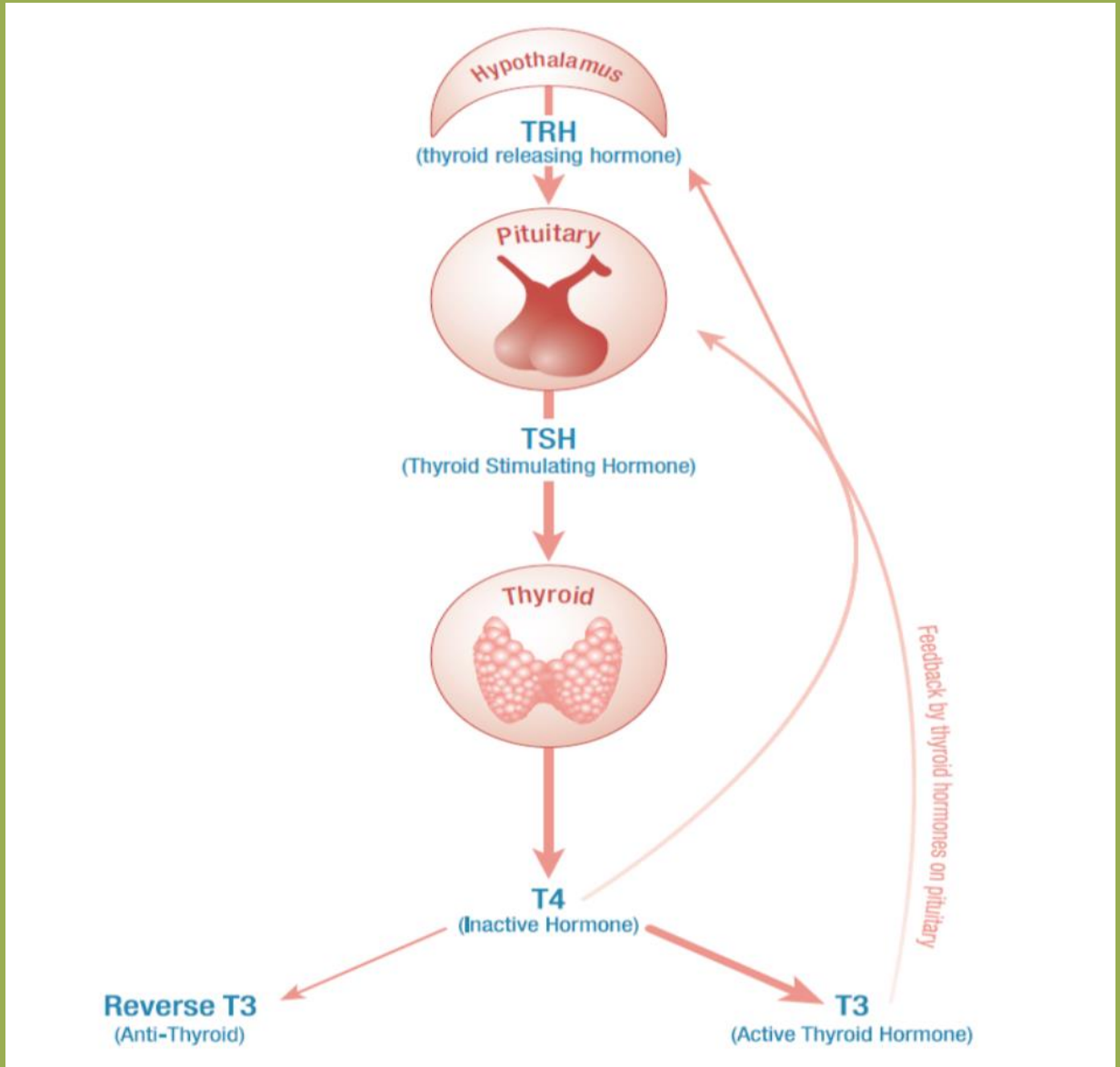
Thyroid Physiology

(without physiologic stress)



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What are the required steps for cellular thyroid activity?

- Hypothalamic/pituitary function
- Secretion of TSH
- Thyroid function (secretion of T4)
- Conversion of T4 to T3
- Thyroid hormone transport into cell
- Receptor binding
- Downstream activation
  (post receptor activation)

- Are the abnormalities/dysfunctions present common or uncommon?

What are the required steps for cellular thyroid activity?

- Hypothalamic/pituitary function common
- Secretion of TSH common
- Thyroid function (secretion of T4) not common
- Conversion of T4 to T3 common
- Thyroid hormone transport into cell common
- Receptor binding common
- Downstream activation
  (post receptor activation) Unknown

- Are the abnormalities/dysfunctions present common or uncommon?

Diagnosis of Low Thyroid

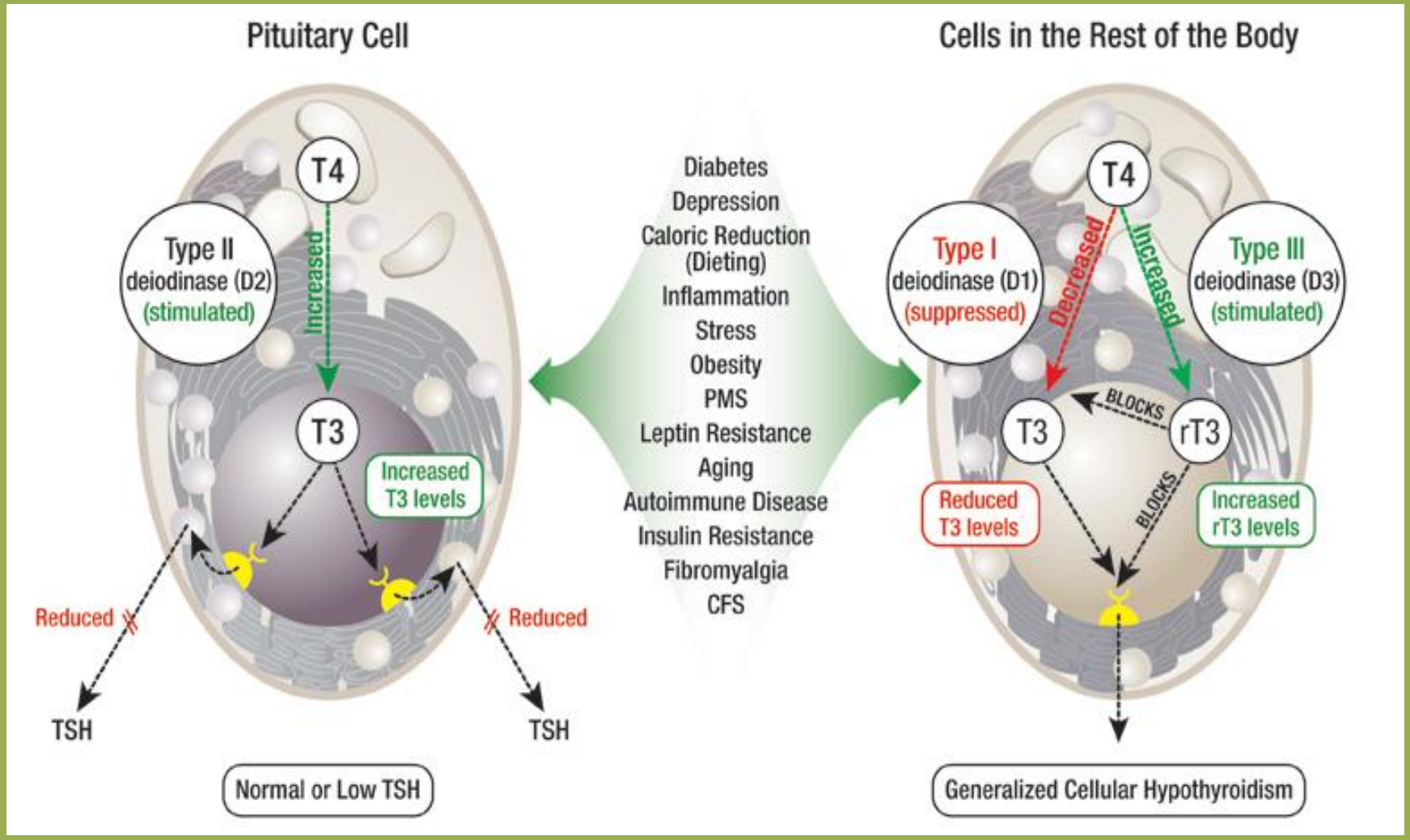
- Standard (traditional) way to diagnose low thyroid is based on an elevation of TSH above 4.2–5.7 (depending on lab results).
- This method misses over 80% of people with low thyroid.
- The patient can complain of numerous symptoms of low thyroid but 90% of doctors will not treat with thyroid because they focus on a normal TSH.

Chronic Non-thyroidal Illness

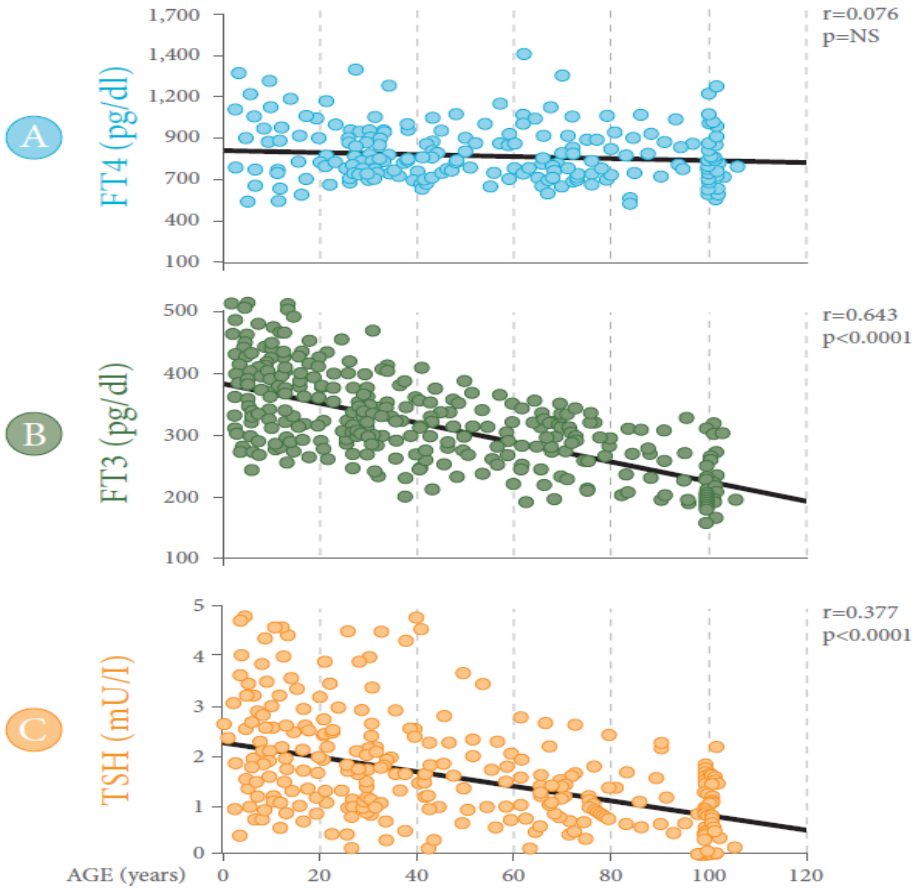
- Studies show that with any inflammation (immune dysfunction) there is a decrease in TSH and T3 and an increase in RT3 due to a suppression and downregulation of D1 and an activation of D2 and D3 (T4 usually slightly increases).
- The more severe the inflammation or immune dysfunction, the more severe the suppression.
- Chronic non-thyroidal illness (decreased tissue T3 levels) occur with response to physiologic and emotional stress;[11-22] depression;[23-45] dieting; [46-51] weight gain and leptin resistance;[47-91] insulin resistance, obesity, and diabetes;[91-99] inflammation from autoimmune disease or systemic illness;[11,100,102-115] chronic fatigue syndrome and fibromyalgia;[121-125] chronic pain;[116-120] and exposure to toxins and plastics.[126-134]
- In the presences of such conditions there are reduced tissue levels of active thyroid in all tissues except the pituitary.
- LDN could potentially improved the abnormal inflammation and immune dysfunction seen with the above conditions, and thus, improve the reduced tissue T3 levels seen with the above conditions

References: Understanding Local Control of Thyroid Hormones: (Deiodinases Function and Activity)

Why the TSH is Unreliable?



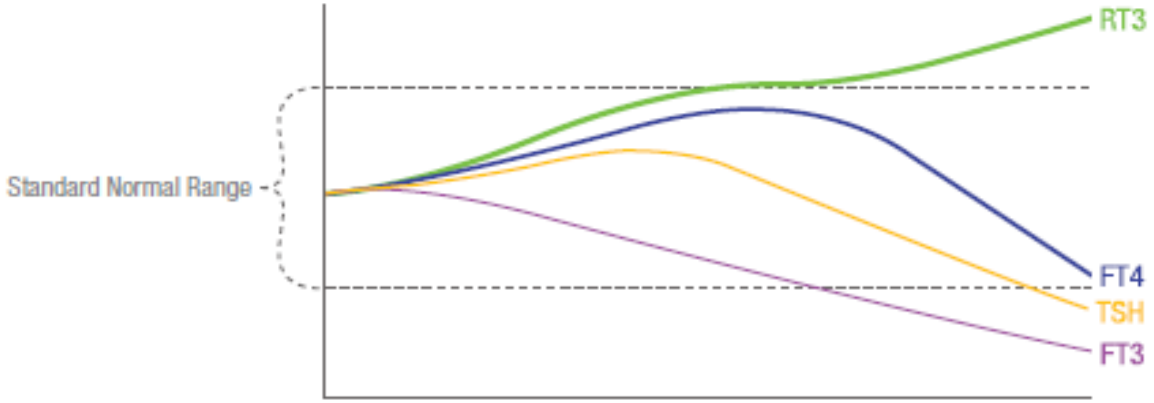
Age dependent variations in mean serum levels of Free T4 (A), Free T3 (B) and TSH (C) in healthy individuals-a combined analysis of the literature. Demonstrates that TSH is not a reliable marker of active thyroid (T3) levels (low T3 levels are associated with decreased, not increased, TSH levels).



1. Schwartz E, Holtorf, K. Hormones in Wellness and Disease Prevention: Common Practices, Current State of the Evidence, and Questions for the Future. Prim Care Clin Office Pract 2008;35:669–705
2. Mariotti S, Barbesino G, Caturegli P, et al. Complex alteration of thyroid function in healthy centenarians. J Clin Endocrinol Met 1993;77(5):1132.
3. Verheecke, P. Free triiodothyronine concentration in serum of 1050 euthyroid children is inversely related to their age. Clin Chem 1997;43(6): 963-967.
4. Quest Diagnostics assay validation free T3, free T4 and TSH, San Juan Capistrano, CA
5. Jankowska H. The effect of age on parameters of thyroid function. Endokrynol Pol. 1993;44(2):117-27.

Associated serum thyroid levels with progressively decreasing tissue thyroid levels due to stress, illness, depression, calorie reduction or aging (Why standard blood tests lack sensitivity to detect low thyroid in the presence of such conditions)

Demonstrates why TSH levels lack the accuracy to detect cellular levels and the free T3/reverse T3 ratio is the most accurate method to determine cellular thyroid levels in the presence of physiologic stress, illness, depression or obesity.



Severity of illness/depression stress/calorie reduction	none	mild	moderate	severe
Normal aging	young	middle	older	elderly
Tissue hypothyroidism (diminished tissue T3 level)	none/mild	mild/moderate	moderate/severe	severe
Inaccuracy of TSH and T4 levels	none	potentially significant	significant	substantial
Diminished utilization of T4	none/mild	mild/moderate	moderate/severe	severe

Accuracy of TSH in Fibromyalgia

- **TRH testing of FM patients.**
- **Found that all of the patients with fibromyalgia were hypothyroid despite the fact that standard thyroid function tests, including TSH, T4 and T3, were in the normal range.**
- **They found that these patients tended to have low normal TSH levels that averaged 0.86 vs 1.42 in normals with high normal free T4 and low normal T3 levels so doctors erroneously feel these patients are on the high side of normal because of the low normal TSH and high normal T4.**

Neeck G, Riedel W. Thyroid function in patients with fibromyalgia syndrome. *J Rheum* 1992;19(7):1120-1122

Accuracy of TSH in Fibromyalgia Patients

Thyroid Function in Patients with Fibromyalgia Syndrome

GUNTHER NEECK and WALTER RIEDEL

Abstract. Thyroid function was tested in 13 female patients with primary fibromyalgia syndrome (FS) and 10 healthy age matched controls by intravenous injection of 400 μg thyrotropin-releasing hormone (TRH). Basal thyroid hormone levels of both groups were in the normal range. However, patients with primary FS responded with a significantly lower secretion of thyrotropin and thyroid hormones to TRH, within an observation period of 2 h, and reacted with a significantly higher increase of prolactin. Total and free serum calcium and calcitonin levels were significantly lower in patients with primary FS, while both groups exhibited parathyroid hormone levels in the normal range. (*J Rheumatol* 1992;19:1120-2)

Key Indexing Terms:
FIBROMYALGIA SYNDROME TRH TSH PROLACTIN CALCIUM
THYROID HORMONES CALCITONIN PARATHYROID HORMONE

Accuracy of TSH in Chronic Fatigue

- **A study published in *The Lancet* performed thyroid biopsies in patients with chronic fatigue and found that 40% of these patients had lymphocytic thyroiditis.**
- **Only 40% of those with lymphocytic thyroiditis were positive for TPO or antithyroglobulin antibodies or had an abnormal TSH.**
- **Thus, the thyroid dysfunction would have gone undetected in the majority of patients if the biopsy had not been done.**
- **This study also demonstrated that because the TSH is a poor indicator of thyroid function, it also does not predict whose symptoms will respond to thyroid replacement.**
- **The authors state, "After treatment with thyroxine, clinical response was favorable, irrespective of baseline TSH concentration."**

Wikland B. Fine needle aspiration cytology of the thyroid in chronic fatigue. *Lancet* 2001:357:956-57.
Wikland B, *et al*. Subchemical hypothyroidism. *Lancet* 2003;361:1305.

Accuracy of TSH with PMS

- A study published in the *New England Journal of Medicine* investigated the incidence of hypothyroidism in women with PMS using TRH testing.
- It was found that 94% of patients with PMS had thyroid dysfunction (tissue hypothyroidism) compared to 0% of the asymptomatic patients.
- 65% of the hypothyroid patients had thyroid tests in “normal” range and could only be diagnosed by TRH testing (missed by the usual thyroid function tests).
- Gold *et al* found that all PMS patients had a significant improvement in symptoms with thyroid treatment even though the standard blood tests were “normal.”

Gold MS, *et al*. Hypothyroidism and PMS. *JAMA* 1981;245(19):1919-1922.

Accuracy of TSH with PMS

- A study published in the *American Journal of Psychiatry* also investigated thyroid function in women with PMS with the use of TRH testing.
- The study found 70% of women with PMS had abnormal TRH testing, showing thyroid dysfunction despite having normal TSH levels.

Roy-Byrne PP, *et al.* TSH and prolactin responses to TRH in patients with premenstrual syndrome. *Am J Psychiatry* 1987;144(4):480-484.

Accuracy of TSH with Obesity

- A study in the *Journal of Endocrinology and Metabolism* examined the accuracy of using the TSH to identify hypothyroidism in obese individuals via TRH testing.[113]
- The study found that although the TSH levels were not significantly different between normal weight and obese individuals…
- 36% of obese patients had severe thyroid dysfunction not detected by standard TSH testing.

Donders S H. Disparity of thyrotropin (TSH) and TSH-releasing hormone in obesity. *JCEM* 1985;61(1):56-9.

Accuracy of TSH with Obesity

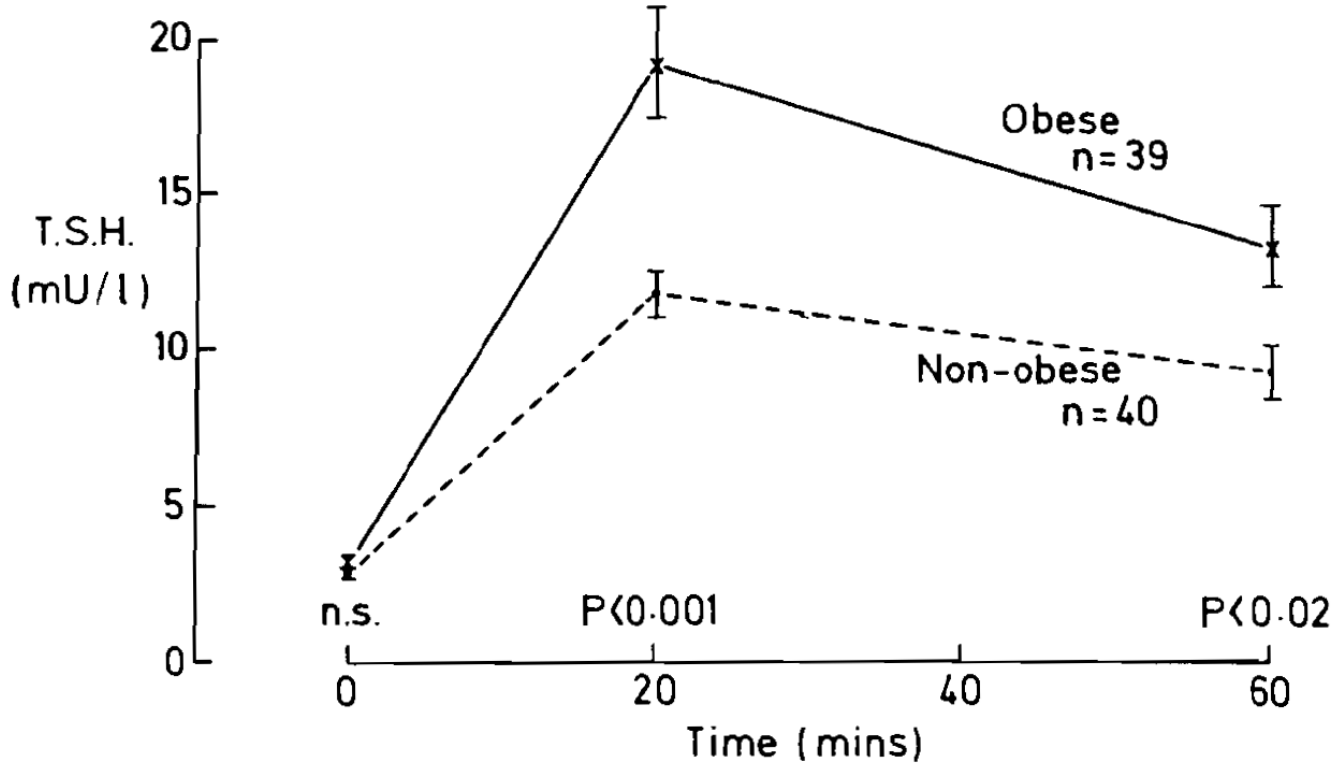


Fig. Mean TSH response (± s.e.) to TRH stimulation in obese and non-obese women

Ford MJ, *et al*. TSH response to TRH in substantial obesity. *Int J Obesity* 1980;4:121-125.

Thyroid levels with insulin resistance and diabetes

- Insulin resistance, diabetes and metabolic syndrome are associated with a significant inflammation and immune dysfunction and resultant reduction in T4 to T3 conversion, an intracellular deficiency of T3, and an increased conversion of T4 to reverse T3.[91,100,92,94,147,184-193,235]
- Additionally, the elevated insulin will increase D2 activity and suppress TSH levels. [91-99,233]

References: Diagnosis of hypothyroidism:
Are we getting what we want from TSH testing?

Thyroid levels with insulin resistance and diabetes

- Diabetic individuals have a 42% reduction in T4 to T3 to T3 conversion.

Pittman CS, *et al*. Abnormalities of thyroid hormone turnover in patients with diabetes mellitus before and after insulin therapy. *JCEM* 1979;48(5):854-60.

Thyroid levels with insulin resistance and diabetes

- Investigation of T4 to T3 conversion in 50 diabetic patients compared to 50 non-diabetic controls. There was no difference in TSH and free T4 levels, but significantly decrease free T3 levels ($p = 0.0001$) that averaged 46% less than controls.
- The FT3/FT4 ratio was 50% less in diabetic patients versus controls. The TSH failed to elevate despite the fact that serum T3 was approximately half of normal.
- Saunders J, *et al* also found that diabetics had approximately a 50% reduction in T3 levels and significantly increased reverse T3 levels and decreased T3/reverse T3 ratios.

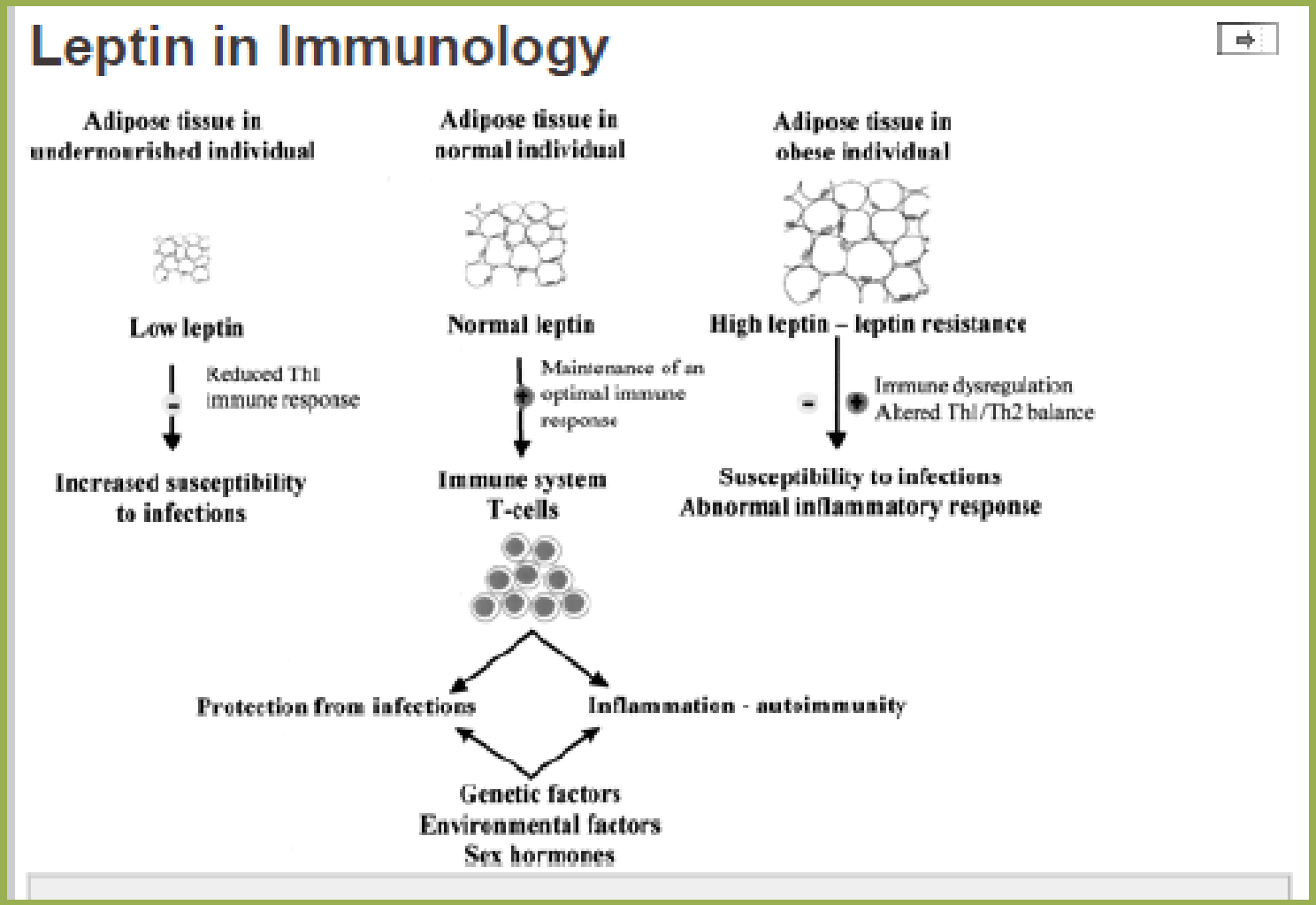
- Islam S, *et al*. A comparative study of thyroid hormone levels in diabetic and non-diabetic patients. *SE Asian J Trop Med Public Health* 2008;39(5):913-916.
- Saunders J. *et al*. Thyroid hormones in insulin requiring diabetes before and after treatment. *Diabetologia* 1978;15:29-32.

Thyroid and leptin

- Leptin is a major regulator of body weight and metabolism
- Leptin promotes TH1 cell differentiation and cytokine production
- Leptin resistance, and associated decreased TH1/TH2 ratio, is shown to suppress D1 and stimulate D2, resulting in reduced cellular T3 but a reduction in serum TSH.[47,84-89]

Matarese G, Moschos S, Mantzoros CS. Leptin in Immunology. J of Immunology

Thyroid and leptin



Matarese G, Moschos S, Mantzoros CS. Leptin in Immunology. J of Immunology 2005;174(6):3137-3142

Diagnosis
(leptin)

- The metabolic effects of leptin resistance include a diminished TSH secretion, a suppressed T4 to T3 conversion, an increase in reverse T3, an increase in appetite, an increase in insulin resistance and an inhibition of lipolysis (fat breakdown).[1-29,31]
- These effects of leptin resistance on thyroid hormones contribute to the drop in TSH and T3 levels that occur with dieting and results in decreased tissue thyroid action and a depressed metabolic rate that inhibits weight loss and promotes weight gain.[1,6,10,14,18-23,29,30-37]
- LDN can improve leptin resistance
- TSH is not reliable if leptin level is above 12
- LDN should be considered in patients with elevated leptin levels above 12

References: Endocrinological Assessment and Treatment of Weight Gain & Obesity

Reverse T3 and leptin

- Physiologic reversal of leptin resistance restored deiodinase activity except in the presence of elevated reverse T3.[86]

Cettour-Rose P, *et al*. Central stimulatory effect of leptin on T3 production is mediated by brown adipose tissue type II deiodinase. *Am J Physiology Endocrinol Metab* 2002;283(5):E980-7

Thyroid Hormone Transport

- In order to have biological activity, the T4 and T3 must, however, cross the cellular membrane from the serum into the target cells.
- This “free hormone” or “diffusion hypothesis” was formulated in 1960 and assumes the concentration of free hormones (free T4 and free T3) in the serum determines the rate and extent of uptake into the cell and thus intracellular thyroid hormone concentration.

References: Thyroid Hormone Transport

Thyroid Hormone Transport

- That hypothesis has been shown to be totally incorrect.[1-67]

References: Thyroid Hormone Transport

Thyroid Hormone Transport

- Because thyroid cellular transport is energy dependent, any condition associated with a reduced production of the cellular energy (mitochondrial dysfunction) will also be associated with reduced transport of thyroid into the cell, resulting in cellular hypothyroidism despite having standard blood tests in the “normal” range.

References: Thyroid Hormone Transport

Thyroid Hormone Transport

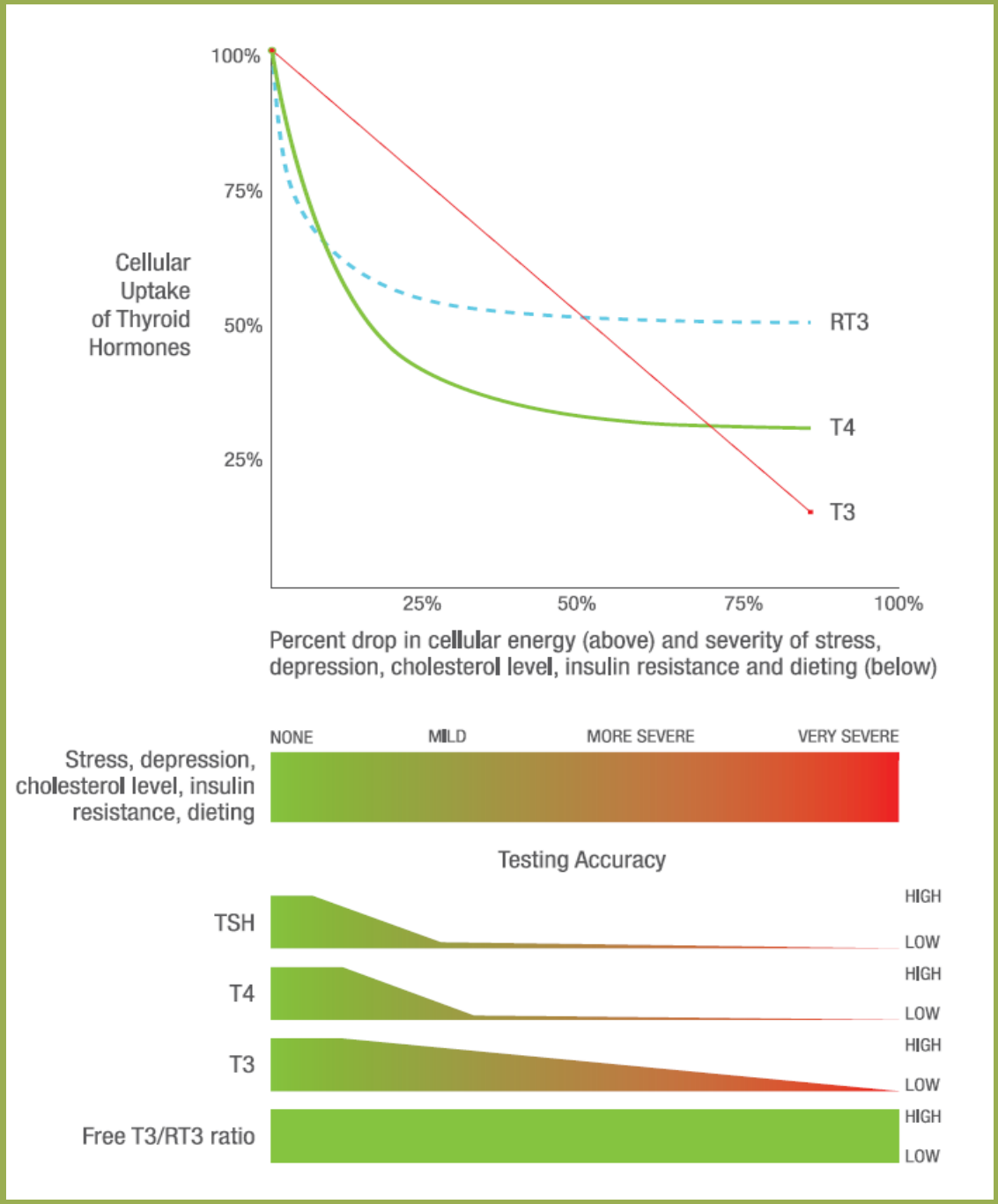
- Conditions associated with reduced mitochondrial function, inflammation or immune dysfunction are associated with impaired thyroid transport
- Conditions include insulin resistance, diabetes and obesity;[68,69,71,70,73,74,75,76,106] diabetes;[69,73,74,75,76] neurodegenerative diseases;[73,83,84,85,86,87)] aging;[73,74,88-100] chronic fatigue syndrome; [73,101,102] fibromyalgia; [73,103,104] migraines; [73] chronic infections; [73] cardiovascular disease; [73,99,104,105,108] and nflammation and chronic illness; [73,109,110,111]
- Thus, standard blood tests can be very unreliable if any of these commonly occurring conditions are present and therapies that reduce inflammation (such as LDN) would be expected to improve dysfunctional thyroid transport.[1-107]

References: Thyroid Hormone Transport

Thyroid Hormone Transport

- Specific and separate transporters for T4 and T3.
- The transporter for T4 is much more energy dependent than the transporter for T3[5,40,41,49,52,53,66] (see Figure 1).
- Even slight reductions in cellular energy (mitochondrial function) results in dramatic declines in the uptake of T4 while the uptake of T3 is much less affected.[5,41,62,67]
- Pituitary has completely different transporters that are not energy dependent.

References: Thyroid Hormone Transport


100%
75%
50%
25%
Cellular Uptake of Thyroid Hormones
RT3
T4
T3
25%
50%
75%
100%
Percent drop in cellular energy (above) and severity of stress, depression, cholesterol level, insulin resistance and dieting (below)
NONE
MILD
MORE SEVERE
VERY SEVERE
Stress, depression, cholesterol level, insulin resistance, dieting
Testing Accuracy
TSH
T4
T3
Free T3/RT3 ratio
HIGH
LOW

Thyroid Hormone Transport (pituitary)

- The pituitary is different than every cell in the body [1,17,43,50,52,55,59,60,61]
  - Different deiodinases.
  - Different high affinity thyroid receptors.
  - Different thyroid transporters that are not energy dependent.
- Pituitary will maintain or increase the uptake of T4 and T3 in low energy states, whereas the rest of the body will have significantly reduced transport of T4 and T3 causing intracellular hypothyroidism.[1,17,22,43,50,52,55,59,60,61]

References: Thyroid Hormone Transport

Thyroid Hormone Transport (pituitary)

- Thyroid transport into the pituitary was increased when the rest of cells have a decreased transport.
- The TSH decreased even when serum levels were decreased by 50% due to increased pituitary thyroid transport.

St Germain DL, Galton VA. Comparative study of pituitary-thyroid hormone economy in fasting and hypothyroid rats. *J Clin Invest* 1985;75(2):679–688.

Thyroid Hormone Transport (pituitary)

THYROID
Volume 6, Number 4, 1996
Mary Ann Liebert, Inc.

Different Regulation of Thyroid Hormone Transport in Liver and Pituitary: Its Possible Role in the Maintenance of Low T_3 Production during Nonthyroidal Illness and Fasting in Man

MARIA E. EVERTS, MARION DE JONG, CHEN-FEE LIM,[1] ROELOF DOCTER, ERIC P. KRENNING, THEO J. VISSER, and GEORG HENNEMANN

ABSTRACT

Nonthyroidal illness (NTI) and fasting in man are characterized by a low serum concentration of T_3 and an increased serum concentration of rT_3. Since the serum level of T_3 is one of the most important factors that determine the metabolic rate, the low serum T_3 during NTI or fasting results in reduction of the energy consumption of the body. This can be regarded as an adaptive mechanism to save energy, and thus to conserve protein and to protect organ function. The low serum T_3 concentration should preferentially be maintained until recovery from illness or adequate calorie supply. This implies that the low serum T_3 should not result in a rise in serum TSH. We postulate that different regulation of thyroid hormone transport into the relevant tissues, i.e., liver and pituitary, may play a role in maintenance of the low T_3 production during NTI and fasting. This hypothesis is further elaborated in this paper by comparing (i) the properties of the thyroid hormone uptake mechanism in rat and human hepatocytes, perfused rat liver, and rat anterior pituitary cells, and (ii) the effects of fasting and conditions that mimic NTI on thyroid hormone transport in the same preparations. In addition, the consequences of changes in thyroid hormone transport and peripheral thyroid hormone metabolism during fasting and NTI for the serum level of rT_3 and for TSH secretion are discussed. The data are compatible with the existence of different transport systems for thyroid hormone in liver and pituitary. We suggest that these different thyroid hormone carriers allow tissue-specific regulation of the intracellular availability of T_3.

Pituitary shown to have different transporters than peripheral tissues (liver tested in this study)

St Germain DL, Galton VA. Comparative study of pituitary-thyroid hormone economy in fasting and hypothyroid rats. J Clin Invest 1985;75(2):679–688.

Thyroid Hormone Transport (pituitary)

"These observations lend further support to the view that thyroid hormone transport into the pituitary is regulated differently than that in the liver." [50]

Wassen FWJS, *et al*. Thyroid hormone uptake in cultured rat anterior pituitary cells: effects of energy status and bilirubin. *J Endocrinol* 2000;165:599-606

Reverse T3

(blocks cellular uptake of T4 and T3)

Placenta (1999), 20, 65–70

Uptake of Reverse T_3 in the Human Choriocarcinoma Cell Line, JAr

A. M. Mitchell[a,d], S. W. Manley[b], K. A. Rowan[a] and R. H. Mortimer[a,c]

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Departments of [b] Physiology and Pharmacology, and [c] Obstetrics and Gynaecology, The University of Queensland, 4072, Australia

Paper accepted 13 July 1998

The uptake and e ux of reverse triiodothyronine (rT_3) in JAr cells were investigated. Uptake of ^{125}I-rT_3 was time dependent and reversible with a saturable component of around 70 per cent of total uptake after 30 min of incubation. E ux was not saturable. Kinetic analysis of the initial specific uptake rates revealed an uptake process with a Michaelis constant of 3.04 ± 0.53 µ (mean ± , $n=15$) and a corresponding maximum velocity of 9.65 ± 2.49 pmol/min/mg protein ($n=15$). Uptake of rT_3 was stereospecific, but not specific for rT_3, as unlabelled stereoisomers of thyroid hormone analogues were more e ective as inhibitors of ^{125}I-rT_3 uptake than rT_3. Unlabelled T_3 and thyroxine (T_4) (10 µ) reduced cellular uptake of ^{125}I-rT_3 by around 82 and 74 per cent, respectively. The calculated inhibition constants K_i were 1.23 ± 0.29 µ ($n=4$) and 0.66 ± 0.19 µ ($n=4$) for T_3 and T_4, respectively. Similarly, rT_3 reduced cellular uptake of ^{125}I-T_3 and ^{125}I-T_4 by 34 and 23 per cent, respectively. The calculated inhibition constants K_i were 1.75 ± 0.55 µ ($n=8$) and 1.08 ± 0.36 µ ($n=8$) for the inhibition of ^{125}I-T_3 and ^{125}I-T_4 uptake, respectively. Reverse T_3 inhibited e ux of ^{125}I-T_3 from the cells by around 20 per cent, but did not inhibit e ux of ^{125}I-T_4. These results suggest that uptake of rT_3 in JAr cells may occur via a single, saturable membrane carrier, which also interacts with T_3 and T_4, while e ux of rT_3 may occur by passive di usion.
Placenta (1999), 20, 65–70

Reverse T3 blocked cellular uptake of T3 by 34% and T4 by 23%.

Thyroid Hormone Transport

- When cell cultures are incubated with the serum from physiologically stressed or dieting individuals; there is shown to be a dramatic reduction of the uptake of T4 by the cells that correlates with the degree of stress (immune dysfunction).[41,42,50]

References: Thyroid Hormone Transport

Thyroid Hormone Transport (stress)

- Serum from non-stressed individuals had no effect on T4 cellular uptake, whereas those with significant physiologic stress had up to a 44% reduction in T4 uptake into the cell.
- It was shown that the free T3/reverse T3 ratio was the most accurate marker for reduced cellular uptake of T4.

Vos RA *et al*. Impaired thyroxine and 3,5,3'-triiodothyronine handling by rat hepatocytes in the presence of serum of patients with nonthyroidal illness. *J Clin Endocrinol Metab* 1995;80:2364-2370.

Thyroid Hormone Transport (reverse T3)

- How do you tell if you have reduced thyroid transport?
  - Remember symptoms number one key-(labs support)!
  - RT3—The transporter for reverse T3 (rT3) has the same pharmacodynamics and kinetics as the T4.[6,41,45,62,66,67]
  - Main reason that rT3 goes up with stress, etc. is reduced transport.
  - This property makes it the most useful indicator of diminished transport of T4 into the cell (signs and symptoms).[45]

References: Thyroid Hormone Transport

Thyroid Resistance

- General term-Thyroid in blood has less effect.
- Can be secondary to reduced T4 to T3 conversion, reduced transport, receptor blockage (toxin, genetics or infection) or reduced translation.
- Clinical diagnosis-No blood tests will detect resistance, but can give clues.
- Can overcome the resistance with increasing levels of T3 or can remove resistance by reducing immune dysfunction/inflammation with LDN or treating underlying cause of the immune dysfunction/inflammation

Thyroid Resistance

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Medical Hypotheses (2003) **60**(2), 175–180

doi:10.1016/S0306-9877(02)00353-5

Type I interferons induce proteins susceptible to act as thyroid receptor (TR) corepressors and to signal the TR for destruction by the proteasome: possible etiology for unexplained chronic fatigue

P. Englebienne, M. Verhas, C. V. Herst, K. De Meirleir

University of Brussels (ULB/VUB), and RED Laboratories, N.V., Brussels, Belgium

Summary In some patients complaining of chronic fatigue such as those suffering from the chronic fatigue syndrome (CFS), no underlying physical cause can be clearly identified and they typically present a normal thyroid function. Several studies indicate a dysregulation in the type I interferons (IFN-α/β) pathway in CFS resulting in a sustained upregulation of 2′,5′-oligoadenylate synthetases (2-5OAS). Likewise, patients treated with IFN-α/β usually complain of severe fatigue as a limiting side effect. Beside the 2-5OAS, IFN-α/β induce also the expression of three closely related proteins of unknown function termed the 2-5OAS-like (2-5OASL) proteins. The amino acid sequences of the 2-5OASL proteins display 96% identity with the partial sequence of the thyroid receptor interacting protein (TRIP) 14, further contain two typical thyroid hormone receptor (TR) coregulator domains and feature two ubiquitin C-terminal domains. From these observations, we raise the hypothesis that the 2-5OASL proteins are TRIPs capable of, respectively, repressing TR transactivation and/or signaling the receptor for destruction by the proteasome. Such molecular mechanisms could explain the development of a clinical hypothyroid state in presence of a normal thyroid function.

Immune activation in CFS suppresses activation of thyroid receptor

Thyroid Resistance

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A metabolic basis for fibromyalgia and its related disorders: the possible role of resistance to thyroid hormone

R. L. Garrison, P. C. Breeding

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Summary It has long been recognized that the symptom complex of fibromyalgia can be seen w
hypothyroidism. Hypothyroidism may been categorized, like diabetes, into type I (hormone deficient) and type II (hormone resistant). Most cases of fibromyalgia fall into the latter category. The syndrome is reversible with treatment, and is usually of late onset. It is likely more often acquired than due to mutated receptors. Now that there is evidence to support the hypothesis that fibromyalgia may be due to thyroid hormone resistance, four major questions appear addressable. First, can a simple biomarker be found to help diagnose it? Second, what other syndromes similar to Fibromyalgia may share a thyroid-resistant nature? Third, in non-genetic cases, how is resistance acquired? Fourth, what other methods of treatment become available through this new understanding?

Preliminary evidence suggests that serum hyaluronic acid is a simple, inexpensive, sensitive, and specific test that identifies fibromyalgia. Overlapping symptom complexes suggest that chronic fatigue syndrome, Gulf war syndrome, premenstrual syndrome, post traumatic stress disorder, breast implant silicone sensitivity syndrome, bipolar affective disorder, systemic candidiasis, myofascial pain syndrome, and idiopathic environmental intolerance are similar enough to fibromyalgia to merit investigation for possible thyroid resistance. Acquired resistance may be due most often to a recently recognized chronic consumptive coagulopathy, which itself may be most often associated with chronic infections with mycoplasmids and related microbes or parasites. Other precipitants of thyroid resistance may use this or other paths as well. In addition to experimentally proven treatment with supraphysiologic doses of thyroid hormone, the thyroid-resistant disorders might be treatable with anti-hypercoagulant, anti-infective, insulin-sensitizing, and hyaluronolytic strategies.

A wide-range of chronic illnesses, including FM and CFS, are associated with chronic infections causing immune activation of coagulation resulting in an acquired thyroid resistance.

Treatment with heparin,, LDN and "superphysiologic" doses of T3 can be effective in reducing thyroid resistance

CFS/FM

- Almost all CFS/FM are low thyroid.
- Combination of secondary/tertiary/reduced T4 to T3 conversion/increased rT3/reduced thyroid transport and thyroid hormone resistance.
- LDN potentially beneficial in CFS/FM through increased tissue T3 levels

Diagnosis
(SHBG)

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Age modulates effects of thyroid dysfunction on sex hormone binding globulin (SHBG) levels

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Key words: Aging, SHBG, thyroid dysfunction, hypothyroidism, hyperthyroidism

Summary: Symptoms of thyroid dysfunction are difficult to detect in elderly people and TSH is sometimes unreliable. We therefore tested the value of SHBG as a marker of thyroid hormone action on the liver to determine the thyroid status of elderly people. Aging euthyroid men and women have a significant increase in SHBG ($p > 0.0001$). In aging women the decrease in SHBG with hypothyroidism and increase with hyperthyroidism are highly significant ($p < 0.0001$ and $p < 0.0005$ respectively). No significant variation in SHBG was observed in men with thyroid dysfunction. SHBG can help to determine the thyroid status of aging women.

SHBG can be used as a measure of tissue thyroid levels.

In young women, average SHBG was 24 in hypo, 43 in euthyroid and 153 in hyperthyroid patients.

In older women SHBG averaged 37 in hypo, 69 in euthyroid and 115 in hyperthyroid patients.

In younger men, SHBG averaged 15 in hypo, 27 in euthyroid and 107 in hyperthyroid patients.

In older men, SHBG averaged 42 in hypo, 54 in euthyroid and 83 in hyperthyroid patients.

Can also be helpful for follow-up as a marker and support for adequate replacement.

Diagnosis
(SHBG)

Sex Hormone-Binding Globulin in the Diagnosis of Peripheral Tissue Resistance to Thyroid Hormone: The Value of Changes after Short Term Triiodothyronine Administration*

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ABSTRACT. Thyroid hormone is one of several factors that modulate the level of sex hormone-binding globulin (SHBG) in serum. SHBG levels are usually elevated in thyrotoxicosis and have been reported to be normal in a few patients with generalized resistance to thyroid hormone (GRTH). This study was designed to determine whether basal serum SHBG levels or the SHBG response to short term T_3 administration could be used as an index of thyroid hormone action and thus serve as a test for the evaluation of patients suspected of having peripheral tissue resistance to thyroid hormone. Serum SHBG, total T_4, free T_4 index (FT_4I), total T_3, and TSH levels were measured in 21 normal subjects, 28 hypothyroid patients, 20 thyrotoxic patients, and 10 patients with GRTH.

Excluding patients with GRTH, serum basal SHBG values were correlated with FT_4I values ($r = 0.66$; $P < 0.0001$). Mean SHBG levels in the patients with GRTH [37.6 ± 16.2 (±SD) nmol/L] were not significantly different from those in the normal subjects (35.1 ± 19.3 nmol/L) or hypothyroid patients (26.3 ± 17.1 nmol/L), but were significantly lower than those in the thyrotoxic group (64.7 ± 19.2 nmol/L; $P < 0.001$). All 10 patients with GRTH had basal SHBG values in the normal range, but 7 of 20 (35%) thyrotoxic patients also had normal basal SHBG values.

T_3 was given orally for three sequential 3-day periods at doses of 50, 100, and 200 μg daily to 7 normal subjects, 11 hypothyroid and 3 thyrotoxic patients, and all 10 patients with GRTH. The serum SHBG concentration was measured on the last day at each dosage level. During T_3 administration, SHB
creased in all individuals with normal tissue respons
increase above the basal value (ΔSHBG) at each
similar in normal, hypothyroid, and thyrotoxic indivi
resistant subjects). After administration of 50 μg T_3 da
mean ΔSHBG level was decreased [−2.9 ± 5.3 (±SD) nmol/L] in the resistant patients and increased (4.6 ± 4.9 nmol/L; $P < 0.005$) in the nonresistant subjects. After administration of 100 μg T_3 daily, the mean ΔSHBG was −4.5 ± 6.8 nmol/L in the resistant patients and 8.6 ± 5.1 nmol/L ($P < 0.0001$) in the nonresistant subjects. Serum SHBG decreased by more than 2 nmol/L in 6 of 10 (60%) resistant patients, but in no nonresistant subject. After administration of 200 μg T_3 daily, the mean ΔSHBG increase was 0.7 ± 7.3 nmol/L in the resistant patients and 16.6 ± 7.3 nmol/L ($P < 0.0001$) in the nonresistant subjects.

Neither the combination of a normal basal serum SHBG value and elevated serum thyroid hormone values nor the relationship between serum SHBG and FT_4I values was sufficient to separate all GRTH patients from those with thyrotoxicosis. The combination of elevated serum thyroid hormone values and failure of serum SHBG to increase above the basal value after the administration of T_3 for 6 days was found in 9 of 10 patients with GRTH but in none of the thyrotoxic subjects. The response of SHBG to T_3 administration is useful in the demonstration of peripheral tissue resistance to thyroid hormone. (*J Clin Endocrinol Metab* **66**: 740, 1988)

SHBG will increase with the use of LDN or the administration of T3 or with in normal individuals but not in those with thyroid resistance

Conclusions

(LDN & thyroid):

- LDN can be effective for autoimmune thyroiditis.
- LDN can potentially improve tissue thyroid levels in conditions associated with immune dysfunction and inflammation by improving thyroid resistance (due to reduced T4 to T3 conversion, impaired thyroid transport and leptin resistance).

Thank you

I will be available outside for questions
Also, studies and references available at www.NAHypothyroidism.org