References 7

Links, Abstracts, Articles, etc.

These links should work as of 2014; sometimes you have to click on them several times; if they don't work, then Google/search the titles

Thyroid Associated Conditions, Thyroid General, UCP's, Hashi's, Cannabis, T1AM, Peroxidases, MOA's,

http://www.eje-online.org/content/168/1/R13.full.pdf Role of emotional stress in the pathophysiology of Graves' disease

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1941994/ Antibodies targeting the calcium binding skeletal muscle protein calsequestrin are specific markers of ophthalmopathy and sensitive indicators of ocular myopathy in patients with Graves' disease

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC506356/ Fibrosis of the Thyroid and Lacrimal Glands. "*HASHIMOTO (1912) remarked on the similarity of the form of thyroiditis, described by him and now known by his name, to the lesions of Mikulicz's disease, which include a chronic inflammatory reaction in the lacrimal glands. Only recently, however, has evidence accumulated of a true association between non-infective chronic inflammatory lesions of the thyroid and lacrimal glands (Anderson, Gray, Beck, and Kinnear, 1961; Bunim, 1961). We record here a case in which an inflammatory lesion of the thyroid, considered to be Riedel's thyroiditis, was followed by fibrous replacement of the thyroid and both lacrimal glands . . . The interest of the present case is that an uncommon lesion of the thyroid-total hyaline fibrosis with focal calcification-is exactly duplicated by an equally uncommon lesion of the lacrimal glands.*"

http://www.iovs.org/content/48/7/3038.long Influence of Thyroid Hormone on Thyroid Hormone Receptor Beta 1 Expression and Lacrimal Gland and Ocular Surface Morphology. "*Chronically reduced levels of TH lead to biochemical and structural changes and modulate the levels of Thrb in LG. These events confirm that LG is a target organ for TH and may facilitate understanding of the mechanism related to dry eye in hypothyroidism.*"

http://www.ncbi.nlm.nih.gov/pubmed/837917 Role of Thyroid Gland on the Peroxidase and Iodinating Enzymes of Submaxillary Gland. "*The present evidence indicates that the level of iodinating activity of the rat submaxillary gland is under control of the thyroid gland, on thyroidectomy increasing about 4-fold and this increase is prevented by administration of thyroxine (Table 2). Restoration of the enzyme activities almost to the normal levels by administration of thyroxine, as shown in this paper, rules out any possible involvement of the parathyroid in the modulation of submaxillary peroxidase activityin the above conditions."*

http://www.degruyter.com/view/j/mjms.2009.2.issue-3/MJMS.1857-5773.2009.0059/mjms.1857-5773.2009.0059.xml Thyroid Dysfunction in Patients with Systemic Connective Tissue Disease. "*Thyroid dysfunction was common in patients with SCTD and they were associated with antithyroid antibodies".*

http://www.hindawi.com/journals/jdr/2013/390534/ The Relationship between Type 2 Diabetes Mellitus and Related Thyroid Diseases. *"Type 2 diabetes mellitus (T2DM) has an intersecting underlying pathology with thyroid dysfunction. The literature is punctuated with evidence indicating a contribution of abnormalities of thyroid hormones to type 2 DM . . . Insulin resistance is also associated with thyroid dysfunction. Hyper- and hypothyroidism have been associated with insulin resistance which has been reported to be the major cause of impaired glucose metabolism in T2DM. The state-of-art evidence suggests a pivotal role of insulin resistance in underlining the relation between T2DM and thyroid dysfunction. A plethora of preclinical, molecular, and clinical studies have evidenced an undeniable role of thyroid malfunctioning as a comorbid disorder of T2DM. It has been investigated that specifically designed thyroid hormone analogues can be looked upon as the potential therapeutic strategies to alleviate diabetes, obesity, and atherosclerosis (My note: unintentional analogues [FQ's?] can be looked upon as total endocrine disrupters too). These molecules are in final stages of preclinical and clinical evaluation and may pave the way to unveil a distinct class of drugs to treat metabolic disorders*."

http://circ.ahajournals.org/content/116/15/1725.full Thyroid Disease and the Heart. "*The cardiovascular signs and symptoms of thyroid disease are some of the most profound and clinically relevant findings that accompany both hyperthyroidism and hypothyroidism . . . It has long been recognized that some of the most characteristic and common signs and symptoms of thyroid disease are those that result from the effects of thyroid hormone on the heart and cardiovascular system".*

http://www.wesupportandywakefield.com/documents/ImmunGlutSenBeyond.pdf The immunology of gluten sensitivity beyond the intestinal tract. "*Thyroid autoimmunity is another example of an autoimmune disease that is associated with celiac disease . . . CD and autoimmune thyroid disorders share a common genetic predisposition, namely, the DQ2 allele. This common predisposing genetic background would explain the higher incidence of thyroid autoimmune disorders in CD than in the general population*".

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2384067/ Possible association between thyroid autoimmunity and Menière's disease. "*Overall, our data demonstrate a significant association between*

MD and thyroid autoimmunity, which suggests that an autoimmune factor is involved in the aetiopathogenesis of this disease".

http://ajcn.nutrition.org/content/80/4/1050.long Phenotypic expression of the methylenetetrahydrofolate reductase 677C→T polymorphism and flavin cofactor availability in thyroid dysfunction. "*Thyroid status affects the phenotypic expression of the MTHFR 677C→T polymorphism, possibly by modifying the availability of flavin cofactors".*

http://www.ncbi.nlm.nih.gov/pubmed/17584697 Evaluation of thyroid dysfunction in patients with paroxysmal atrial fibrillation. "*Thyroid dysfunctions have a high prevalence in AF patients and hyperthyroidism is the most common disorder. Hyperthyroidism in AF patients more often occurs in women than in men. Any minimal but persistent modification of circulating thyroid hormone levels can favor episodes of AF; it can be useful to thoroughly assess thyroid function in all patients suffering from AF".*

http://www.biomed.cas.cz/physiolres/pdf/57%20Suppl%201/57_S119.pdf Immunoprotective Steroids and SHBG in Non-Treated Hypothyroidism and their Relationship to Autoimmune Thyroid Disorders

http://www.ncbi.nlm.nih.gov/pubmed/7485204 Autoimmune Thyroid Disease in Primary Sjogren's Syndrome. "*The high prevalence of autoimmune thyroid disease and thyroid dysfunction found in primary Sjögren's syndrome, using sensitive immunologic and thyroid function tests, suggest that both diseases are more frequently associated than it was previously thought, and should be sought clinically and by laboratory tests in all patients with primary Sjögren's syndrome*".

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3838329/ Thyroid hormones and tendon: current views and future perspectives. Concise review. "*Recent study demonstrated the presence of TRs (thyroid hormone receptors) in tendons and their possible role in the proliferation and apoptosis of human tenocyte isolated from tendon. We review new discovery that revisit our current thinking on the tendon biology focusing on thyroid hormones (THs) T3 and T4, and their possible role on human tenocyte."*

http://www.ncbi.nlm.nih.gov/pubmed/21996646 Thyroid Adverse Effects of Psychotropic Drugs: A Review

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2527361/ Influx of recent thymic emigrants into autoimmune thyroid disease glands in humans. "*Autoimmune thyroid diseases (AITD) are considered as prototypic organ-specific autoimmune diseases, yet their underlying aetiology remains poorly understood. Among the various pathophysiological mechanisms considered, a failure of central tolerance has received little attention. Here we present evidence in favour of dysregulated thymic function playing a role in AITD"* (My note: my thymus gland is heavily involved with my AITD, so I know the association is true anyway).

http://online.liebertpub.com/doi/abs/10.1089/thy.2009.0383 Graves' Disease and Thymic Hyperplasia: The Relationship of Thymic Volume to Thyroid Function

http://www.surgjournal.com/article/S0039-6060(13)00506-0/abstract Graves' disease and thymic hyperplasia

http://ehealthforum.com/health/thyroid-thymus-masses-t199843.html Forum discussion on thyroid and thymus.

http://www.ncbi.nlm.nih.gov/pubmed/10090312 Expression of thyroid-related genes in human thymus. *"There are several thyroid antigens including human sodium iodide symporter (hNIS), thyrotropin receptor (TSH-R), thyroid peroxidase (TPO), and thyroglobulin (Tg) that have been considered to be thyroid-specific proteins involved in the pathogenesis of autoimmune thyroid diseases . . . RT-PCR and Southern hybridization revealed expression of each of these 4 thyroid-related genes in normal human thymus. In addition, immunohistochemical analysis of frozen tissue sections derived from normal human thymus showed marked immunoreactivity for NIS, TSH-R, and Tg as well as weaker staining for TPO. Control reactions using isotype matched nonimmune immunoglobulins were consistently negative. Taken together, our results suggest that NIS-, TSH-R-, TPO-, and Tg-RNA are present and actively processed to immunoreactive NIS-, TSH-R-, TPO-, and Tg-like protein in human thymus. These data support the concept that pre-T lymphocytes may be educated to recognize thyroid-related epitopes expressed in thymus, and, thus, to generate self-tolerance against these thyroid-related antigens."*

http://www.hormones.gr/205/article/article.html Thyroid hormones and aging

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1340780/ Resolution of dyskinesia and the "on-off" phenomenon in thyrotoxic patients with Parkinson's disease after antithyroid treatment

Link didn't work, but I have the paper: Rapid Nongenomic Effects of 3,5,3-Triiodo-L-Thyronine on the Intracellular pH of L-6 Myoblasts Are Mediated by Intracellular Calcium Mobilization and Kinase Pathways

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC371980/ Stimulation by Triiodothyronine of the In Vitro Uptake of Sugars by Rat Thymocytes

http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0063282 Serum LAIR-2 Is Increased in Autoimmune Thyroid Diseases. " *Inhibitory signals are required to terminate an immune response and to prevent excessive immune reactions or autoimmune disease. These signals can be provided by inhibitory immunoreceptors, often containing immunoreceptor tyrosine-based inhibitory motifs (ITIMs) in their cytoplasmic tails . . . The leukocyte-associated Ig-like receptor is a small family of ITIM-containing inhibitory receptor, belonging to the Ig superfamily [5]. LAIR-2, is a secreted molecule, whereas LAIR-1 is its membrane bound homologue, LAIR-2 is believed to play a regulatory role in the interaction between collagen and LAIR-1 [6,7] . . . Recently, collagens were identified as natural, high-affinity ligands for LAIR molecules [9]. Interaction of LAIR-1 with collagens directly inhibits immunocyte activation in vitro and may represent a key mechanism of peripheral immune regulation through extracellular matrix [9]. Given the broad expression profile of LAIR-1 [5] and the abundance of collagen in the human body, a fine-tuned regulation of collagen-LAIR-1 interaction is likely needed. As above mentioned, the soluble LAIR-2 molecule present in the plasma and interstitial fluid is likely to play a significant role in such regulation . .*

. Autoimmune thyroid diseases (ATD), namely, autoimmune (Hashimoto's) thyroiditis and Graves' disease, are the most frequent organspecific autoimmune diseases, and autoimmune thyroiditis is regarded as a prototype of such pathological conditions. Here we report the presence of high levels of LAIR-2 in sera of patients with autoimmune thyroid diseases."

http://www.ncbi.nlm.nih.gov/pubmed/14688214 Immunohistochemical Assessment of the Peripheral Benzodiazepine Receptor in Human Tissues. "*Since its identification in 1977, the peripheral benzodiazepine receptor (PBR) has been the subject of intensive research to define its function. The protein was first described as a peripheral binding site for the benzodiazepine diazepam (Braestrup and Squires 1977) and has been reported to be involved in a variety of biological activities. These include control of steroidogenesis and apoptotic responses, regulation of cell proliferation, immunomodulation, porphyrin transport and heme synthesis, anion transport, and the modulation of mitochondrial respiration".*

http://www.ncbi.nlm.nih.gov/pubmed/12108519 Endogenous Excitatory Amino Acid Neurotransmission Regulates Thyroid-Stimulating Hormone and Thyroid Hormone Secretion in Conscious Freely Moving Male Rats. "*These results suggest the importance of endogenous EAA in the regulation of hormone secretion from the pituitary-thyroid axis, as well as the role of the N-methyl-D-aspartate (NMDA) and non-NMDA receptors in the stimulatory effect of EAAs on the pituitary-thyroid axis."*

http://press.endocrine.org/doi/abs/10.1210/endo-69-1-55 THE EFFECT OF AGE AND THYROID HORMONES ON THE MONOAMINE OXIDASE OF RAT HEART

http://www.sciencedirect.com/science/article/pii/0003986159901377 Monoamine oxidase activity in liver of thyroid-fed rats

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1776831/pdf/brjpharm00530-0122.pdf An effect of thyroid hormones upon monoamine oxidase activity

http://www.ncbi.nlm.nih.gov/pubmed/2345806 Leakage of thyroid hormone-inducible monoamine oxidase inhibitor from rat liver cytosol.

http://www.ncbi.nlm.nih.gov/pubmed/827361 Influence of thyroid hormones on monoamine oxidase activity in newborn rats.

http://www.ncbi.nlm.nih.gov/pubmed/41907 Selective influences of age and thyroid hormones on type A monoamine oxidase of the rat heart.

http://jhc.sagepub.com/content/48/1/147.full.pdf Localization of Monoamine Oxidase A and B in Human Pancreas, Thyroid, and Adrenal Glands. "*Thyroid gland showed strong MAO-A immunoreactivity in all cell types and was MAO-B-negative."*

Thyroid General (Steroids General Too)

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2852208/ Molecular Aspects of Thyroid Hormone Actions

http://www.ncbi.nlm.nih.gov/pubmed/11117200 Thyroid hormones and their effects: a new perspective. An excellent review and interesting perspective; the entire paper is well worth the read.

http://pharmrev.aspetjournals.org/content/52/4/513.long Multiple Actions of Steroid Hormones—A Focus on Rapid, Nongenomic Effects

http://physrev.physiology.org/content/81/3/1097.long Physiological and Molecular Basis of Thyroid Hormone Action

http://www.thyroidmanager.org/chapter/thyroid-hormone-synthesis-and-secretion/ Thyroid Hormone Synthesis and Secretion

http://www.thyroidresearchjournal.com/content/5/1/3 Phylogenetic analysis of the human thyroglobulin regions

http://www.jstor.org/discover/10.2307/25418468?sid=21105734794491&uid=70&uid=3739256&uid=2129&uid=4&uid=2&uid=3739792 Thyroid Physiology

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4104039/ Clocks for all seasons: unwinding the roles and mechanisms of circadian and interval timers in the hypothalamus and pituitary

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3742223/ (Healthy) Ageing: Focus on Iodothyronines. "*Low thyroid function has been associated with increased longevity in humans [29–31], with a particularly strong case made in the Leiden Longevity study*". Interesting paper.

http://www.thyroidmanager.org/ All the articles here are informative.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1671863/ Response of carpal tunnel syndrome to hormone replacement therapy

http://img.mailchimp.com/2009/03/19/4dac29e167/Cortisol_in_hair.pdf Measurement of Cortisol in Hair: Some Recent Investigations

http://www.ncbi.nlm.nih.gov/pubmed/8592797 Histochemical Study of Cutaneous Mucins inHypothyroid Dogs. "*In these dogs, the only polysaccharidic compound involved in the dermal mucinosis was hyaluronic acid. In this study, hyaluronic acid dermal deposits of hypothyroid dogs were significantly different from those of controls in subepidermal connective tissue and loose reticular connective tissue but not in periadnexal zones.*" (My note: hyaluronic acid and its relationship to tendons; see next).

http://www.hindawi.com/journals/bmri/2014/783632/ The Use of Hyaluronic Acid after Tendon Surgery and in Tendinopathies. "*In quite all the experimental studies, performed after surgical procedures for tendon injuries or in the treatment of chronic tendinopathies, using different hyaluronic acid compounds, positive results (reduced formation of scars and granulation tissue after tendon repair, less adhesions and gliding resistance, and improved tissue healing) were observed. In a limited number of cases, hyaluronic acid has been employed in clinical practice. After flexor tendon surgery, a greater total active motion and fingers function, with an earlier return to work and daily activities, were observed. Similarly, in patients suffering from elbow, patellar, and shoulder tendons disorders, pain was reduced, and function improved. The positive effect of hyaluronic acid can be attributed to the anti-inflammatory activity, enhanced cell proliferation, and collagen deposition, besides the lubricating action on the sliding surface of the tendon.*"

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3230140/ Neurosteroids and GABAA receptor interactions: a focus on stress

Uncoupling Proteins

http://en.wikipedia.org/wiki/Uncoupling_protein Uncoupling protein

http://www.sciencedirect.com/science/article/pii/S001457930300320X Thyroid hormone and uncoupling proteins. "*From an analysis of recent results, it seems clear that UCPs are important mediators of the effects of T3 at the cellular level and that T3 is capable of integrating the various biochemical pathways involved in UCP expression and activity, such as those on lipid metabolism, CoQ levels and ROS production".*

http://www.ncbi.nlm.nih.gov/pubmed/10454126 Thyroid hormone and other regulators of uncoupling proteins.

http://www.ncbi.nlm.nih.gov/pubmed/15072699 Effect of thyroid hormone on uncoupling protein-3 mRNA expression in rat heart and skeletal muscle. "*We conclude that the effect of T3 on UCP-3 expression in cardiac and skeletal muscle is not dependent on either angiotensin II or the beta-adrenergic system and probably reflects a direct action of the hormone on UCP-3 gene expression.*"

Hashi's

https://www.edmcasereports.com/articles/endocrinology-diabetes-and-metabolism-case-reports/10.1530/EDM-14-0037 IgG4-related thyroiditis: a case report and review of literature

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1291772/ Hashitoxicosis and autoantibody interference with thyroid function tests. *"We conclude that in patients with multiple autoantibodies assessment of the wildly fluctuating clinical state may be impossible by standard laboratory tests. Despite spectacular advances in the measurement of hormone concentrations, clinical signs and symptoms still have a role to play in management of patients with thyroid disease."*

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3271310/ Hashimoto's Thyroiditis: From Genes to the Disease. *"Although exact mechanisms of aetiology and pathogenesis of the disorder are not completely understood, a strong genetic susceptibility to the disease has been confirmed predominantly by family and twin studies. Several genes were shown to be associated with the disease occurrence, progression, and severity. Genes for human leukocyte antigen, cytotoxic T lymphocyte antigen-4, protein tyrosine phosphatase nonreceptor-type 22, thyroglobulin, vitamin D receptor, and cytokines are considered to be of utmost importance . . . Environmental factors influencing HT development are iodine intake, drugs, infections and different chemicals. Disturbed self-tolerance accompanied by the increased antigen presentation is a prerequisite for the HT occurrence, whereas proper interaction of thyroid cells, antigen presenting cells, and T cells are necessary for the initiation of thyroid autoimmunity."*

Cannabis

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2828614/ Cannabinoids as novel anti-inflammatory drugs

http://www.ncbi.nlm.nih.gov/pubmed/17626034 The endocannabinoid system is dysregulated in multiple sclerosis and in experimental autoimmune encephalomyelitis

http://www.ncbi.nlm.nih.gov/pubmed/19457575 Cannabinoid-induced apoptosis in immune cells as a pathway to immunosuppression

T1AM

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3473208/ Biosynthesis of 3-Iodothyronamine (T1AM) Is Dependent on the Sodium-Iodide Symporter and Thyroperoxidase but Does Not Involve Extrathyroidal Metabolism of T4. *"T1AM is an endogenous derivative of TH present in rat, mouse, hamster, and human, with acute pharmacological effects. A single pharmacological dose of T1AM results in hypothermia, bradycardia, a shift in the respiratory quotient, hyperglycemia, and hypoinsulinemia within minutes to a few hours. Structural similarities between T4 and T1AM, including the presence of iodine and the biaryl ether carbon skeletons, suggest that T1AM is a metabolite of T4 . . . T1AM is a recently*

discovered endogenous compound that contains the unique chemical signature of a TH, namely a biaryl ether core structure containing an iodine substituent. Like the TH T4 and T3, T1AM is found in various tissues and in circulation (21), and circulating T1AM is largely bound to lipoprotein particles (30). Recent advances in the quantitative analysis of T1AM using methods based on LC-MS/MS and T1AM-specific immunoassay suggest that endogenous T1AM is present in tissues (in the rat) and circulation (in humans) at levels that are comparable with those of total T4 (14, 21). In several rat tissues, including heart, liver, kidney, skeletal muscle, and stomach, T1AM is present at a greater concentration than T3, the major active metabolite of T4 (21) . . . Additionally, a recent report documents that human fibrocytes express thyroglobulin and are able to take up and incorporate [125I] into the protein (40). The expression of these proteins in a cell population outside the thyroid gland creates the possibility that T1AM biosynthesis originates through a de novo pathway involving extrathyroidal iodination and cross-coupling of tyrosine residues.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3265861/ ApoB-100 containing lipoproteins are the major carriers of 3-iodothyronamine in circulation

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2926234/ 3-Monoiodothyronamine: the rationale for its action as an endogenous adrenergic-blocking neuromodulator. "*Extensive deiodinase studies indicated that T1AM was derived from the T4 metabolite, reverse triiodothyronine (revT3), while functional studies provided well-confirmed evidence that T1AM has strong adrenergic blocking effects. Because a state of adrenergic overactivity prevails when triiodothyronine (T3) concentrations becomes excessive, the possibility that T3's metabolic partner, revT3, might give rise to an antagonist of those T3 actions was thought to be reasonable . . . This new evidence points to a physiological role for T1AM as an endogenous adrenergic-blocking neuromodulator in the central noradrenergic system."*

More Thyroid

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2200462/ Autoantibodies to thyroid hormones: the role of thyroglobulin

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3657903/ Glutamic acid decarboxylase (anti-GAD) & tissue transglutaminase (anti-TTG) antibodies in patients with thyroid autoimmunity

http://www.ncbi.nlm.nih.gov/pubmed/22219301 Glutamine and glutamic acid enhance thyroid-stimulating hormone b subunit mRNA expression in the rat pars tuberalis

http://www.ncbi.nlm.nih.gov/pubmed/1673689 Unlike Thyrotropin, Thyroid-stimulating Antibodies do not Activate Phospholipase C in Human Thyroid Slices

http://www.jbc.org/content/242/8/1864.long Action of Phospholipase C on the Thyroid: ABOLITION OF THE RESPONSE TO THYROID-STIMULATING HORMONE

http://www.jimmunol.org/content/176/7/4479.full Iodination of Tyrosyls in Thyroglobulin Generates Neoantigenic Determinants That Cause Thyroiditis. "*Among the known autoantigens, thyroglobulin (Tg)3 is unique in its ability to incorporate and store available iodine in the form of iodotyrosyl residues (1). This process facilitates thyroid hormone, i.e., thyroxine (T4) and triiodothyronine, formation through intramolecular coupling of specific iodotyrosyls, but it also has immunological consequences: enhanced iodination of Tg has been known to increase its immunogenicity at the T and B cell level, as well as its pathogenicity in experimental animals (2–5). The mechanisms underlying these observations remain mostly unknown, but progress with T cell epitope mapping in Tg has recently shed light on some of the processes involved.*"

http://www.ncbi.nlm.nih.gov/pubmed/18308074 Environmental neuroendocrine and thyroid disruption: relevance for reproductive medicine?

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1181904/ A Novel Syndrome Combining Thyroid and Neurological Abnormalities Is Associated with Mutations in a Monocarboxylate Transporter Gene

http://cancerres.aacrjournals.org/content/20/9/1309.full.pdf The Effect of Thyroxine on the Cytochrome C Content of Tissues of Rats Bearing the Walker Carcinosarcoma 256

http://www.ncbi.nlm.nih.gov/pubmed/10719389 Thyroid peroxidase activity is inhibited by amino acids "*As reported here, the enzymatic hydrolysates of TPO preparations and of bovine serum albumin (BSA), as well as some amino acids and peptides can act as TPO iodide oxidation inhibitors, suggesting that a peptide or even some amino acids might interfere with the in vivo TPO iodide oxidation and iodination reactions.*"

http://www.jbc.org/content/260/25/13546.long Thyroid Peroxidase Selects the Mechanism of Either 1- or 2-Electron Oxidation of Phenols, Depending on Their Substituents

http://www.ncbi.nlm.nih.gov/pubmed/7076648 Affinity Chromatography of Thyroid Peroxidase Using Tyrosine Coupled to Agarose

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2315650/ The phylogeny of the mammalian heme peroxidases and the evolution of their diverse functions

http://www.ncbi.nlm.nih.gov/pubmed/23025526 Thyrotropin-Blocking Autoantibodies and Thyroid-Stimulating Autoantibodies: Potential Mechanisms Involved in the Pendulum Swinging from Hypothyroidism to Hyperthyroidism or Vice Versa. "*Thyrotropin receptor (TSHR) antibodies that stimulate the thyroid (TSAb) cause Graves' hyperthyroidism and TSHR antibodies which block thyrotropin action (TBAb) are occasionally responsible for hypothyroidism. Unusual patients switch from TSAb to TBAb (or vice versa) with concomitant thyroid function changes. We have examined case reports to obtain insight into the basis for ''switching . . . whole genome screening of relatively rare ''switch'' patients and appropriate Graves' and Hashimoto's controls could provide unexpected and valuable*

information regarding the basis for thyroid autoimmunity . . . (i) A small proportion of TBAb-positive hypothyroid patients treated with LT4 switch to TSAb and hyperthyroidism; conversely, some Graves' patients treated with anti-thyroid drugs switch from TSAb to TBAb-induced hypothyroidism. (ii) LT4 therapy, often associated with decreased thyroid autoantibodies, in a select patient group induces or enhances thyroid autoantibody levels. In contrast, antithyroid drug treatment usually decreases thyroid autoantibody levels.''

http://joe.endocrinology-journals.org/content/209/3/299.long Vitamin E ameliorates iodine-induced cytotoxicity in thyroid. *"Acute and excessive iodine supplementation leads to iodine-induced thyroid cytotoxicity. Excessive oxidative stress has been suggested to be one of the underlying mechanisms in the development of thyroid cytotoxicity. The aim of this study was to investigate whether vitamin E (VE), an important antioxidant, could ameliorate iodine-induced thyroid cytotoxicity . . . Thyrocytes constantly produce moderate amounts of reactive oxygen species (ROS), which are physiologically required for thyroid hormone synthesis (Denef et al. 1996, Song et al. 2007). Nevertheless, when ROS are over-produced, they may become toxic and damage cell structures and macromolecules including lipids, proteins, and nucleic acids. 4-Hydroxynonenal (4-HNE) is a toxic product resulting from lipid peroxidation and 8-hydroxyguanine (8-OHdG) and is a maker for DNA and RNA damage. A toxic effect of iodide given to iodine-deficient laboratory animals was first noted by Follis (1959). Similar studies have shown that 4-HNE is increased in goitrous and in iodine-induced involuting glands (iodine replenishment for 3 days, acute effects), indicating that oxidative stress (OS) is greatly enhanced in these conditions (Poncin et al. 2008). Increased OS is not necessarily lethal to goitrous cells but is associated with cellular destruction and inflammation in iodine-induced thyroid involution (Mutaku et al. 2002, Poncin et al. 2008). It is therefore crucial for thyrocytes to develop protective mechanisms that limit the toxicity of endogenous and exogenous ROS. Fortunately, several antioxidants including superoxide dismutases, catalase, glutathione peroxidases (GPxs), peroxiredoxins (PRDXs), thioredoxin reductase (TrxR), and vitamin E (VE) are constitutively expressed in the thyroid (Mutaku et al. 2002, Gerard et al. 2005, Kohrle et al. 2005, Schweizer et al. 2008). Without these antioxidants, it would not be possible for these cells to remain viable and function properly."*

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2452979/ Iodine Alters Gene Expression in the MCF7 Breast Cancer Cell Line: Evidence for an Anti-Estrogen Effect of Iodine

http://www.ncbi.nlm.nih.gov/pubmed/16522926 Hypothesis: Dietary Iodine Intake in the Etiology of Cardiovascular Disease

http://www.ncbi.nlm.nih.gov/pubmed/12728462 The effect of iodine restriction on thyroid function in patients with hypothyroidism due to Hashimoto's thyroiditis.

http://www.ncbi.nlm.nih.gov/pubmed/12930600 Effect of Iodine Restriction on Thyroid Function in Patients with Primary Hypothyroidism

http://www.ncbi.nlm.nih.gov/pubmed/12466344 Effects of Chronic Iodine Excess in a Cohort of Long-Term American Workers in West Africa. *"We found that during prolonged excess iodine exposure there were marked increases in serum total iodine concentrations, and the prevalence of goiter, elevated*

serum TSH values, and elevated serum thyroid peroxidase antibody values increased. The prevalence of all abnormalities decreased after removal of excess iodine from the drinking water system."

http://nora.nerc.ac.uk/8354/1/CR03084N.pdf Database of the Iodine Content of Food and Diets Populated with Data From Published Literature

http://www.checkyourneck.com/media/lol-low-iodine-cookbook.pdf The light of life foundation cookbook great recipes for an iodine free diet

http://cancerres.aacrjournals.org/content/35/9/2332.long Rat Mammary Gland Atypia Produced by Iodine Blockade with Perchlorate

http://press.endocrine.org/doi/full/10.1210/en.2006-0203 The Ele*mental* Importance of Sufficient Iodine Intake: A Trace Is Not Enough

http://eje-online.org/content/150/5/605.long The environment and autoimmune thyroid diseases

http://www.jbc.org/content/239/9/3062.long ACTION AND METABOLISM OF THYROID HORMONES AND IODINE-DONATING SUBSTANCES. II. SITE OF ACTION IN THE RESPIRATORY CHAIN.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1810443/ Spreading of antibody reactivity to non-thyroid antigens during experimental immunization with human thyroglobulin. *"Intermolecular spreading of antibody reactivity has been implicated in the evolution of autoimmune disease . . . Tg-immunized animals developed . . . high reactivity to myosin . . ."*

http://www.ncbi.nlm.nih.gov/pubmed/21325460 Current Thyroglobulin Autoantibody (TgAb) Assays Often Fail to Detect Interfering TgAb that Can Result in the Reporting of Falsely Low/Undetectable Serum Tg IMA Values for Patients with Differentiated Thyroid Cancer. *"Many specimens with interfering TgAb were misclassified as TgAb negative using manufacturer-recommended cutoffs. It is recommended that assay AS limits be used to detect TgAb to minimize false-negative misclassifications. However, for two of four assays, AS limits failed to detect interfering TgAb in 20-30% of cases. TgAb methods were too qualitatively and quantitatively variable to establish conversion factors that would allow a change in method without disrupting serial TgAb monitoring."*

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1385257/ Thyroid microsomal/thyroid peroxidase autoantibodies show discrete patterns of cross-reactivity to myeloperoxidase, lactoperoxidase and horseradish peroxidase. *"The recent cloning of the thyroid peroxidase (TPO) has shown that it is identical to the thyroid microsomal antigen (TMA), a potent antigen involved in autoimmune thyroid disease (ATD), which shares significant sequence homology with myeloperoxidase. The present study shows that autoantibodies (aAb) to the TMA/TPO antigen cross-react with human leucocyte myeloperoxidase, bovine lactoperoxidase and horseradish peroxidase . . . compelling evidence on the genuine cross-reactive nature of these aAbs. Sera from different patients contain different qualitative and quantitative specificities ofaAb to the TMA/TPO antigen, confirming the polyclonal nature of this autoimmune response."*

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1385181/ Autoantibodies to the thyroid microsomal/thyroid peroxidase antigen are polyclonal and directed to several distinct antigenic sites. "*Our results demonstrate the the autoimmune response to thyroid microsomal antigen/thyroid peroxidase (TMA/TPO) is multifocal and far more heterogeneous than hitherto recognized . . . The data support the view that the autoimmune reactivity to the TMA/TPO is a specific polyclonal response with a minimum of six distinct, independent determinants that are recognized by aAbs.*"

http://www.altmedrev.com/publications/11/4/330.pdf 5-Methyltetrahydrofolate Monograph: Alternative Medicine Review

http://www.ncbi.nlm.nih.gov/pubmed/9253347 Immunoglobulin Gk Antithyroid Peroxidase Antibodies in Hashimoto's Thyroiditis: Epitope-Mapping Analysis

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2200393/ Thyroid peroxidase autoantibody epitopic 'fingerprints' in juvenile Hashimoto's thyroiditis: evidence for conservation over time and in families. *"In conclusion, TPO autoantibody epitopic fingerprints are frequently conserved over many years. Studies on additional families are necessary to establish whether or not the epitopic profiles of TPO autoantibodies are inherited."*

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2893665/ N-Acetylcysteine and 15 Deoxy-12,14-Prostaglandin J2 Exert a Protective Effect Against Autoimmune Thyroid Destruction in Vivo but Not Against Interleukin-1/Interferon -Induced Inhibitory Effects in Thyrocytes in Vitro

https://suite.io/sarah-tomley/3ypj206 How NAC and Glutathione Can Help to Heal Hashimoto's Disease

http://www.ncbi.nlm.nih.gov/pubmed/22800594 Studies of fluoride on the thyroid cell apoptosis and mechanism.

http://www.ncbi.nlm.nih.gov/pubmed/22186223 Short-term effects of combined treatment with potassium bromide and methimazole in patients with Graves' disease. *"Treatment of patients with Graves' disease with a novel combination therapy consisting of potassium bromide and methimazole resulted in a rapid improvement in clinical symptoms and decreased blood thyroid hormone levels to homeostatic levels faster than methimazole treatment alone*."

http://www.annalsafrmed.org/article.asp?issn=1596-3519;year=2008;volume=7;issue=2;spage=88;epage=90;aulast=Bello-Sani Myasthenia gravis associated with autoimmune thyroid disease: A report of two patients

http://www.ncbi.nlm.nih.gov/pubmed/15255296 The effect of bromide on the ultrastructure of rat thyrocytes. *"Electron microscopic examination of thyroid tissue following administration of bromide to rats showed marked hypertrophy and hyperplasia in the thyrocytes, microfollicular rearrangement and lowered volume of colloid . . . These changes, with previously published light microscopical, radioanalytical and biochemical findings, confirm the goitrogenic effect of bromide."*

Peroxidases

http://what-when-how.com/molecular-biology/peroxidase-molecular-biology/ Peroxidases

http://www.ncbi.nlm.nih.gov/pubmed/11087769?dopt=Abstract MPO and APOEepsilon4 polymorphisms interact to increase risk for AD in Finnish males.

http://www.jleukbio.org/content/77/5/598.short Myeloperoxidase: friend and foe. "*This review will consider the potential sources of H2O2 for the MPO-H2O2-halide system; the toxic products of the MPO system; the evidence for MPO involvement in the microbicidal activity of neutrophils; the involvement of MPO-independent antimicrobial systems; and the role of the MPO system in tissue injury. It is concluded that the MPO system plays an important role in the microbicidal activity of phagocytes*." (Good article)

http://www.jci.org/articles/view/116531 Tyrosyl radical generated by myeloperoxidase catalyzes the oxidative cross-linking of proteins

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2118127/ Killing controversy. "Neutrophils are short-lived phagocytes. As the primary microbe-killing cells of the innate immune system, they contain small vesicle packets, or granules, of deadly toxins. These granules fuse with phagosomes containing engulfed bacteria and deliver their fatal payload. But which of the granules' contents are doing the killing, and how?

http://www.researchgate.net/publication/23104439_Lactoperoxidase-catalysed_iodine_metabolism_in_human_saliva Lactoperoxidase-catalysed iodine metabolism in human saliva.

http://www.madsci.org/posts/archives/2006-08/1156791277.Bc.r.html Re: How does lactoperoxidase label Tyrosine residues? (My note: consider FQ's acting as aromatic amines → eventually, initiating autoimmune/hypersensitivity rxns).

http://www.ncbi.nlm.nih.gov/pubmed/2912960?dopt=Abstract Studies on the mechanism of the iodination of tyrosine by lactoperoxidase. "*Studies with lactoperoxidase showed that a highly reactive intermediate is produced (on the enzyme) from I- and H2O2 which then diffuses from the enzyme and very rapidly and indiscriminately iodinates any Tyr or peptides containing Tyr which are in the same solution.*"

http://www.ncbi.nlm.nih.gov/pubmed/3520291 Salivary peroxidases. "*Peroxidases are known to be involved in the intracellular metabolism of H2O2 coupled with various physiological functions. Apart from the thyroid gland, the enzyme has been isolated from various extrathyroidal sources of which salivary gland is one of the richest sources of the enzyme . . . The possible function of the enzyme in iodine metabolism and in bactericidal action has been discussed.*"

http://www.jbc.org/content/271/7/3406.full.pdf Spectral Analysis of Lactoperoxidase: EVIDENCE FOR A COMMON HEME IN MAMMALIAN PEROXIDASES

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2740456/ Binding Modes of Aromatic Ligands to Mammalian Heme Peroxidases with Associated Functional Implications

http://www.ncbi.nlm.nih.gov/pubmed/7714125?dopt=Abstract Human monoclonal autoantibodies against the immunodominant region on thyroid peroxidase: lack of cross-reactivity with related peroxidases or thyroglobulin and inability to inhibit thyroid peroxidase enzymatic activity. "*Thyroid peroxidase (TPO) autoantibodies are heterogeneous and have been classified in terms of whether they cross-react with myeloperoxidase (MPO), lactoperoxidase (LPO), or thyroglobulin (Tg) as well as by whether they inhibit TPO enzymatic activity . . . Consequently, our data suggest that TPO autoantibodies that cross-react with MPO, LPO, or Tg, or inhibit TPO enzymatic activity are likely to bind outside the immunodominant region*."

http://www.ncbi.nlm.nih.gov/pubmed/1318692 Myeloperoxidase-catalyzed iodination and coupling. "*Myeloperoxidase (MPO), which displays considerable amino acid sequence homology with thyroid peroxidase (TPO) and lactoperoxidase (LPO), was tested for its ability to catalyze iodination of thyroglobulin and coupling of two diiodotyrosyl residues within thyroglobulin to form thyroxine*."

http://www.ncbi.nlm.nih.gov/pubmed/1898006 Peroxidase-catalyzed bromination of tyrosine, thyroglobulin, and bovine serum albumin: comparison of thyroid peroxidase and lactoperoxidase. "*Measurements of thyroid:serum concentration ratios for 82Br- in similar rats provided no evidence that Br- is a substrate for the iodide transport system of the thyroid*."

http://www.ncbi.nlm.nih.gov/pubmed/6094529 Mechanisms of thyroid peroxidase- and lactoperoxidase-catalyzed reactions involving iodide. "*An essential feature of the scheme was the proposal that enzyme-bound hypoiodite, designated [EOI]-, is a common intermediate in various peroxidase-catalyzed reactions involving iodide.*"

http://www.ncbi.nlm.nih.gov/pubmed/11080366?dopt=Abstract Molecular evolution of the myeloperoxidase family. *"Animal myeloperoxidase and its relatives constitute a diverse protein family, which includes myeloperoxidase, eosinophil peroxidase, thyroid peroxidase, salivary peroxidase, lactoperoxidase, ovoperoxidase, peroxidasin, peroxinectin, cyclooxygenase, and others. The members of this protein family share a catalytic domain of about 500 amino acid residues in length, although some members have distinctive mosaic structures*."

http://www.ncbi.nlm.nih.gov/pubmed/6266056 The control of peroxidase-catalysed iodination and de-iodination. *"It has been demonstrated that the H2O2/l ratio is a critical factor in the control of iodination and de-iodination of covalently bound tyrosyl residues in proteins and free iodotyrosines by peroxidase enzymes. This has been shown for myeloperoxidase (MPO) isolated from normal human polymorphonuclear lymphocytes in particular, and also for peroxidase of animal origin such as thyroid peroxidase (TPO) and lactoperoxidase (LPO). It has been shown that the H2O2/l ratio exerts a controlling influence on MPO-catalysed reactions of fully iodinated tyrosines, e.g. di-iodotyrosine, and of partially and completely iodinated thyronines such as thyroxine and tri-iodothyronine. Using an in vivo model system it has been shown that MPO catalyses the sequential events of iodination, iodine exchange and de-iodination of tyrosines and, furthermore, that all three reactions are influenced by the rate of H2O2*

generation and the iodide concentration of the reaction medium. The action of MPO on iodothyronine substrates only affects de-iodination irrespective of whether the iodothyronine is partially iodinated, as in tri-iodothyronine, or completely iodinated, as in thyroxine. This MPO-catalysed de-iodination of thyroxine and tri-iodothyronine can also be regulated by the H2O2/l ratio. Moreover, the results show that MPO-catalysed iodine exchange can only occur in completely iodinated tyrosines such as di-iodotyrosine (DIT). Iodine exchange in partially iodinated tyrosines such as mono-iodotyrosine (MIT) or in iodothyronines (T3 and T4) cannot be catalysed by MPO irrespective of the H2O2/l ratio. These results introduce a new concept which may be important in understanding the control of thyroid activity in thyroid disease and the control of MPO activity in biological defence mechanisms in man." (My note: ROS production of H2O2 too much, or too little, or ratio of H2O2 is off, iodination and de-iodination cannot occur; fits with ROS model of FQT).

http://www.ncbi.nlm.nih.gov/pubmed/8243270 Human thyroid peroxidase-myeloperoxidase chimeric molecules: tools for the study of antigen recognition by thyroid peroxidase autoantibodies.

http://www.ncbi.nlm.nih.gov/pubmed/9246211 Antibody reactivity against thyroid peroxidase and myeloperoxidase in autoimmune thyroiditis and systemic vasculitis. *"The results suggest that TPO and MPO molecules contain cross-reactive epitopes that are exposed in denaturated molecules and may thus cause false positive antibody findings in solid phase EIA assays."*

http://www.ncbi.nlm.nih.gov/pubmed/11217812 Absence of cross-reactivity to myeloperoxidase of anti-thyroid microsomal antibodies in patients with autoimmune thyroid diseases. "*We conclude that there is no cross-reactivity to MPO of TMA in patients with autoimmune thyroid diseases, possibly because of difference in the spatial configuration of the immunodominant region."*

http://www.ncbi.nlm.nih.gov/pubmed/9189013 Some anti-thyroperoxidase antibodies positive sera give a pANCA pattern on ethanol-fixed human neutrophils: cross-reactivity or false positives?

http://www.ihop-net.org/UniPub/iHOP/gs/92814.html TPO

http://jasn.asnjournals.org/content/13/7/1977.long ANCA Are Pathogenic—Oh Yes They Are!

http://www.ncbi.nlm.nih.gov/pubmed/24986845 Clinical and pathological features of microscopic polyangiitis in 20 children.

http://www.revistanefrologia.com/modules.php?name=articulos&d_op=&idarticulo=10841&idlangart=EN&preproduccion= Chronic pulmonary bleeding as the first sign of microscopic polyangiitis associated with autoimmune thyroiditis

http://www.ncbi.nlm.nih.gov/pubmed/8199304 Inhibition of peroxidase-catalyzed reactions by arylamines: mechanism for the anti-thyroid action of sulfamethazine. "*Sulfonamide antibiotics, typified by sulfamethazine (SMZ), are widely used in veterinary practice. Sulfonamide residues in milk and meat products are of regulatory concern since SMZ is a thyroid carcinogen in rodents and sulfonamide-induced hypersensitivity reactions, including hypothyroidism, have been reported in humans. SMZ and other primary arylamines inhibited iodination reactions catalyzed by thyroid peroxidase (TPO) and the closely*

related lactoperoxidase (LPO) . . . These observations suggest that the primary mechanism for sulfonamide-induced hypothyroidism is reversible inhibition of TPO-mediated thyroid hormone synthesis and not the formation and covalent binding of reactive N-oxygenated metabolites. These results are consistent with a hormonal mechanism for SMZ-induced thyroid carcinogenesis mediated by thyroid-stimulating hormone (TSH).”

http://www.ncbi.nlm.nih.gov/pubmed/8068644 Mechanism-based inactivation of lactoperoxidase and thyroid peroxidase by resorcinol derivatives. “Humans are exposed to resorcinol derivatives in the environment through ground water, foods, food additives, drugs, and hair dyes. Epidemiological studies have linked human exposure to phenolic compounds with the thyroid disorder, goiter. The results presented here demonstrate the suicide (mechanism-based) inactivation of thyroid peroxidase (TPO) and the closely related lactoperoxidase (LPO) by resorcinol derivatives. The evidence for this mechanism includes irreversible, hydrogen peroxide-dependent loss of enzymatic activity by kinetics consistent with a suicide mechanism, concomitant with changes in the visible spectrum of the prosthetic heme group and covalent binding of resorcinol . . . The oxidation of thyroid peroxidase and lactoperoxidase by hydrogen peroxide produces catalytic intermediates containing unpaired electron density on amino acid residues similar to that seen with cytochrome c peroxidase. These results provide an explanation for the potency of resorcinol derivatives in the inhibition of LPO and TPO and the goitrogenic responses observed in humans and animals. The widespread occurrence of resorcinol derivatives in the environment suggests that exposure to these compounds may cause thyroid dysfunction in humans.”

http://www.humanpathol.com/article/S0046-8177(03)00676-2/abstract Ultrastructural localization of thyroid peroxidase, hydrogen peroxide-generating sites, and monoamine oxidase in benign and malignant thyroid diseases

Abstracts, T1AM, DI’s, TH transport, connective tissue, adrenergic

Public release date: 16-May-2004
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New compound may act to keep thyroid activity in check

OHSU study finds T1 amine rapidly causes hypothermia, blood pressure drop, slow pulse (My note: de-iodinases → increased T1 amines → "crashes" that patients experience? Or, conversely, during acute phase of thyrotoxicosis-like symptoms, not enough T1 amine to offset TH? –if de-iodinases don't work?)

PORTLAND, Ore. – Researchers have isolated a naturally occurring, thyroid hormone-derived compound that produces an inactive, torpid-like state in rodents and could someday help doctors stabilize surgical and trauma patients.

Although the compound, 3-iodothyronamine – T1 amine, for short – is a derivative of thyroxine, an essential thyroid hormone that influences development, body temperature, metabolic rate and cardiac performance, it has the opposite effect of thyroxine, according to a study by scientists at Oregon Health & Science University, the University of California, San Francisco (UCSF) and Universita di Pisa, Italy.

The new findings suggest that T1 amine affects several organ systems. Consequently, if its molecular and cellular actions can be precisely described, physicians will be in a better position to treat a variety of cardiovascular and endocrine diseases, as well as mental health disorders, said David Grandy, Ph.D., associate professor of physiology and pharmacology, and cell and developmental biology in the OHSU School of Medicine.

"Here we thought we knew thyroid hormone so well, only to find out there's this whole new aspect of it," said Grandy, co-author of a study published in today's online edition of the journal Nature Medicine. T1 amine's "normal function in the body may be to counteract, or keep in check, thyroid hormone's actions."

In mice, T1 amine can induce profound hypothermia, slow heart rate and drop blood pressure, suggesting that it, or related molecules, might provide a valuable new means by which physicians can stabilize patients during surgery and trauma, Grandy said. Within minutes of administering T1 amine, mice appear to go into a "hypometabolic state."

"Although they're inactive and appear to be unmotivated, they definitely are not anesthetized. It almost looks like they're playing dead and have stopped responding to their environment," Grandy said.

T1 amine has a "profound" effect on the heart where it "almost immediately causes a dramatic decrease in pumping and outflow," Grandy said.

Linda Lester, M.D., assistant professor of medicine in the Division of Endocrinology, Diabetes and Clinical Nutrition, OHSU School of Medicine, said physicians have limited means to rapidly reverse the effects of diseases that increase metabolism.

"The compound described in this article could provide a new tool to manage patients in acute hypermetabolic states, including hyperthyroidism," she said. "The effectiveness of this compound in humans would have to be established prior to considering it as a new therapy, but the rodent studies described in this article support further evaluation."

The molecule's structure, its potency and speed of action suggest that it is a previously undiscovered neurotransmitter, said Thomas Scanlan, Ph.D., co-author on the paper and professor of pharmaceutical chemistry and cellular and molecular pharmacology at UCSF. "While changes in hormone levels may take a day to have their effect, neurotransmitters can act within minutes to hours," Scanlan said. "T1 amine acts this quickly, and it has a chemical structure similar to dopamine or serotonin. Since it looks like a neurotransmitter and acts like a neurotransmitter, we hypothesize that it is a neurotransmitter."

Scanlan, an expert on thyroid hormone chemistry and pharmacology, synthesized T1 amine. The researchers at OHSU and UCSF then found that the compound occurs naturally in the brains of rats and guinea pigs, and subsequently in the brains, heart, liver and blood of adult mice.

The prediction and ultimate discovery of T1 amine followed on the heels of a previous discovery made in the Grandy laboratory.

"For us, when we find a new receptor that is made by the body, it means there must be a naturally occurring molecule, or key, that turns it on," Grandy said. "In our efforts to find this receptor's natural key, or ligand, we tested hundreds of compounds. This analysis identified a small set of chemical groups that were important. Our interest turned to thyroid hormone because it contains each of these chemical groups following a simple chemical modification. What we couldn't know ahead of time is that T1 amine would be the best fitting key for our trace amine receptor."

The Grandy lab also was surprised to find that T1 amine's effects on the body were opposite to those associated with thyroid hormone.

Promoting close collaborations between chemists and biologists, like that between researchers at OHSU and UCSF, is a central aim of OHSU's chemical biology initiative, a developing program led by the Department of Physiology and Pharmacology that is to be housed in new research space now under construction on Marquam Hill.

"The program will bring together, on one campus, chemists and biologists who have the common aim of discovering small molecules that are potent regulators of biological processes and, maybe, prototypes for drugs," said David Dawson, Ph.D., professor of physiology and pharmacology, and department chairman.

Demonstrating that T1 amine and the trace amine receptor "talk to one another" may help scientists better understand and treat depression, schizophrenia, movement disorders, obesity, trauma, stroke, diabetes and cardiovascular disease, Grandy said.

Now that the T1 amine compound has been found, and its biological effects observed, Grandy hopes to study its possible connections to drug dependency and other mental health disorders.

"Interestingly, amphetamines and Ecstasy turn this receptor on," he said. "I'd like to think one direction that future studies will take addresses whether or not T1 amine might influence drug-taking behavior."

Other study collaborators included: Katherine Suchland, Paul Kruzich, Dane Crossley II and James Bunzow, Department of Physiology and Pharmacology, OHSU; Matthew Hart, Department of Pharmaceutical Chemistry and Cellular & Molecular Pharmacology, UCSF; Grazia Chiellini, Sabina Frascarelli, Simonetta Ronca-Testoni, Riccardo Zucchi, Dipartimento di Scienze dell'Uomo e dell'Ambiente, Sezione di Biochimica, Universita di Pisa, Italy; Yong Huang and Emil Lin, Department of Biopharmaceutical Sciences, UCSF; and Daniel Hatton, Department of Behavioral Neuroscience, OHSU.

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UCSF – Wallace Ravven, 415-502-1332, WRavven@pubaff.ucsf.edu

Note: Thyronamine refers both to a molecule, and to derivatives of that molecule: a family of decarboxylated and deiodinated metabolites of the thyroid hormones thyroxine (T4) and 3,5,3'-triiodothyronine (T3).

The group includes:

- Thyronamine (T0AM)
- 3-Iodothyronamine (T1AM), which is the most notable one as it is a trace amine found in the nervous system. It is a possible candidate for the natural ligand of the trace amine-associated receptor TAAR1 (TAR1), a G protein-coupled receptor located in the cell membrane[1]
- 3,5-Diiodothyronamine (T2AM)
- 3,5,3'-Triiodothyronamine (T3AM)

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3-Iodothyronamine (T(1)AM): a new chapter of thyroid hormone endocrinology?

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Author information

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Abstract

3-Iodothyronamine (T(1)AM) is an endogenous thyroid hormone derivative with distinct biological effects that are largely opposite those of thyroid hormone. Administration of T(1)AM to rodents results in rapid and profound reduction in body temperature, heart rate, and metabolism. The structural similarities between thyroxine, T(1)AM, and monoamine neurotransmitters suggest an intriguing role for T(1)AM as both a neuromodulator and a hormone-like molecule that may constitute a part of thyroid hormone action. Several recent studies into its molecular mechanisms of action have shown that T(1)AM can target extracellular receptors such as the trace amine-associated receptors and the alpha(2A) adrenergic receptor, modulate the membrane transport of neurotransmitters, and serve as a substrate of specific membrane transport cellular uptake machinery. This review discusses recent T(1)AM studies, focusing on both the observed in vivo effects of T(1)AM administration and its actions at the molecular level.

Mol Biosyst. 2010 Aug;6(8):1403-10. doi: 10.1039/b926588k. Epub 2010 Mar 31.

Transport of thyroid hormones is selectively inhibited by 3-iodothyronamine.

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Author information

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Abstract

Thyroid hormone transporters are responsible for the cellular uptake of thyroid hormones, which is a prerequisite for their subsequent metabolism and action at nuclear thyroid hormone receptors. A recently discovered thyroid hormone derivative, 3-iodothyronamine (T(1)AM), has distinct biological effects that are opposite those of thyroid hormone. Here we investigate the effects of T(1)AM on thyroid hormone transporters using COS-1 cells transfected with the multispecific organic anion transporting polypeptides (OATPs) 1A2, 1B3, and 1C1, as well as the specific thyroid hormone transporters MCT8 and MCT10, and show that T(1)AM displays differential inhibition of T(3) and T(4) cellular uptake by these transporters. T(1)AM inhibits T(3) and T(4) transport by OATP1A2 with IC(50) values of 0.27 and 2.1 microM, respectively. T(4) transport by OATP1C1, which is thought to play a key role in thyroid hormone transport across the blood-brain barrier, is inhibited by T(1)AM with an IC(50) of 4.8 microM. T(1)AM also inhibits both T(3) and T(4) uptake via MCT8, the most specific thyroid hormone transporter identified to date, with IC(50) values of 95 and 31 microM, respectively. By contrast, T(1)AM has no effect on thyroid hormone transport by OATP1B3 and MCT10. Given that OATP1A2, OATP1C1, and MCT8 are all present in the brain, T(1)AM may play an important role in modulating thyroid hormone delivery and activity in specific target regions in the central nervous system.

Endocrinology. 2009 Mar;150(3):1078-83. doi: 10.1210/en.2008-1518. Epub 2009 Jan 29.

Minireview: Pathophysiological importance of thyroid hormone transporters.

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Author information

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Abstract

Thyroid hormone metabolism and action are largely intracellular events that require transport of iodothyronines across the plasma membrane. It has been assumed for a long time that this occurs by passive diffusion, but it has become increasingly clear that cellular uptake and efflux of thyroid hormone is mediated by transporter proteins. Recently, several active and specific thyroid hormone transporters have been identified, including monocarboxylate transporter 8 (MCT8), MCT10, and organic anion transporting polypeptide 1C1 (OATP1C1). The latter is expressed predominantly in brain capillaries and transports preferentially T(4), whereas MCT8 and MCT10 are expressed in multiple tissues and are capable of transporting different iodothyronines. The pathophysiological importance of thyroid hormone transporters has been established by the demonstration of MCT8 mutations in patients with severe psychomotor retardation and elevated serum T(3) levels. MCT8 appears to play an important role in the transport of thyroid hormone in the brain, which is essential for the crucial action of the hormone during brain development. It is expected that more specific thyroid hormone transporters will be discovered in the near future, which will lead to a better understanding of the tissue-specific regulation of thyroid hormone bioavailability.

Trends Endocrinol Metab. 2008 Mar;19(2):50-6. doi: 10.1016/j.tem.2007.11.003.

Thyroid hormone transport in and out of cells.

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Abstract

Thyroid hormone (TH) is essential for the proper development of numerous tissues, notably the brain. TH acts mostly intracellularly, which requires transport by TH transporters across the plasma membrane. Although several transporter families have been identified, only monocarboxylate transporter (MCT)8, MCT10 and organic anion-transporting polypeptide (OATP)1C1 demonstrate a high degree of specificity towards TH. Recently, the biological importance of MCT8 has been elucidated. Mutations in MCT8 are associated with elevated serum T(3) levels and severe psychomotor retardation, indicating a pivotal role for MCT8 in brain development. MCT8 knockout mice lack neurological damage, but mimic TH abnormalities of MCT8 patients. The exact pathophysiological mechanisms in MCT8 patients remain to be elucidated fully. Future research will probably identify novel TH transporters and disorders based on TH transporter defects.

Endocrinology. 2009 Mar;150(3):1097-107. doi: 10.1210/en.2008-1588. Epub 2009 Jan 29.

Minireview: Defining the roles of the iodothyronine deiodinases: current concepts and challenges.

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Abstract

As is typical of other hormone systems, the actions of the thyroid hormones (TH) differ from tissue to tissue depending upon a number of variables. In addition to varying expression levels of TH receptors and transporters, differing patterns of TH metabolism provide a critical mechanism whereby TH action can be individualized in cells depending on the needs of the organism. The iodothyronine deiodinases constitute a family of selenoenzymes that selectively remove iodide from thyroxine and its derivatives, thus activating or inactivating these hormones. Three deiodinases have been identified, and much has been learned regarding the differing structures, catalytic activities, and expression patterns of these proteins. Because of their differing properties, the deiodinases appear to serve varying functions that are important in regulating metabolic processes, TH action during development, and feedback control of the thyroid axis. This review will briefly assess these functional roles and others proposed for the deiodinases and examine some of the current challenges in expanding our knowledge of these important components of the thyroid homeostatic system.

Thyroid. 2005 Aug;15(8):883-97.

Role of thyroid hormone deiodination in the hypothalamus.

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Abstract

Iodothyronine deiodinases (D1, D2, and D3) comprise a family of selenoproteins that are involved in the conversion of thyroxine (T(4)) to active triiodothyronine (T(3)), and also the inactivation of both thyroid hormones. The deiodinase enzymes are of critical importance for the normal development and function of the central nervous system. D1 is absent from the human brain, suggesting that D2 and D3 are the two main enzymes involved in the maintenance of thyroid hormone homeostasis in the central nervous system, D2 as the primary T(3)-producing enzyme, and D3 as the primary inactivating enzyme. While the coordinated action of D2 and D3 maintain constant T(3) levels in the cortex independently from the circulating thyroid hormone levels, the role of deiodinases in the hypothalamus may be more complex, as suggested by the regulation of D2 activity in the hypothalamus by infection, fasting and changes in

photoperiod. Tanycytes, the primary source of D2 activity in the hypothalamus, integrate hormonal and probably neuronal signals, and under specific conditions, may influence neuroendocrine functions by altering local T(3) tissue concentrations. This function may be of particular importance in the regulation of the hypothalamic-pituitary-thyroid axis during fasting and infection, and in the regulation of appetite and reproductive function. Transient expression of D3 in the preoptic region during a critical time of development suggests a special role for this deiodinase in sexual differentiation of the brain

Human fibrocytes coexpress thyroglobulin and thyrotropin receptor.

Fernando R[1], Atkins S, Raychaudhuri N, Lu Y, Li B, Douglas RS, Smith TJ.

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Abstract

Thyroglobulin (Tg) is the macromolecular precursor of thyroid hormones and is thought to be uniquely expressed by thyroid epithelial cells. Tg and the thyroid-stimulating hormone receptor (TSHR) are targets for autoantibody generation in the autoimmune disorder Graves disease (GD). Fully expressed GD is characterized by thyroid overactivity and orbital tissue inflammation and remodeling. This process is known as thyroid-associated ophthalmopathy (TAO). Early reports suggested that in TAO, both Tg and TSHR become overexpressed in orbital tissues. Previously, we found that CD34(+) progenitor cells, known as fibrocytes, express functional TSHR, infiltrate the orbit, and comprise a large subset of orbital fibroblasts in TAO. We now report that fibrocytes also express Tg, which resolves as a 305-kDa protein on Western blots. It can be immunoprecipitated with anti-Tg Abs. Further, (125)iodine and [(35)S]methionine are incorporated into Tg expressed by fibrocytes. De novo Tg synthesis is attenuated with a specific small interfering RNA targeting the protein. A fragment of the Tg gene promoter fused to a luciferase reporter exhibits substantial activity when transfected into fibrocytes. Unlike fibrocytes, GD orbital fibroblasts, which comprise a mixture of CD34(+) and CD34(-) cells, express much lower levels of Tg and TSHR. When sorted into pure CD34(+) and CD34(-) subsets, Tg and TSHR mRNA levels become substantially higher in CD34(+) cells. These findings indicate that human fibrocytes express multiple "thyroid-specific" proteins, the levels of which are reduced after they infiltrate tissue. Our observations establish the basis for Tg accumulation in orbital GD

Scand J Med Sci Sports. 2000 Dec;10(6):312-20.

Structure of the tendon connective tissue. (My note: do fibrocytes/tenocytes take up or use iodine and if so, for what purpose?)

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Abstract

Tendons consist of collagen (mostly type I collagen) and elastin embedded in a proteoglycan-water matrix with collagen accounting for 65-80% and elastin approximately 1-2% of the dry mass of the tendon. These elements are produced by tenoblasts and tenocytes, which are the elongated fibroblasts and fibrocytes that lie between the collagen fibers, and are organized in a complex hierarchical scheme to form the tendon proper. Soluble tropocollagen molecules form cross-links to create insoluble collagen molecules which then aggregate progressively into microfibrils and then into electronmicroscopically clearly visible units, the collagen fibrils. A bunch of collagen fibrils forms a collagen fiber, which is the basic unit of a tendon. A fine sheath of connective tissue called endotenon invests each collagen fiber and binds fibers together. A bunch of collagen fibers forms a primary fiber bundle, and a group of primary fiber bundles forms a secondary fiber bundle. A group of secondary fiber bundles, in turn, forms a tertiary bundle, and the tertiary bundles make up the tendon. The entire tendon is surrounded by a fine connective tissue sheath called epitenon. The three-dimensional ultrastructure of tendon fibers and fiber bundles is complex. Within one collagen fiber, the fibrils are oriented not only longitudinally but also transversely and horizontally. The longitudinal fibers do not run only parallel but also cross each other, forming spirals. Some of the individual fibrils and fibril groups form spiral-type plaits. The basic function of the tendon is to transmit the force created by the muscle to the bone, and, in this way, make joint movement possible. The complex macro- and microstructure of tendons and tendon fibers make this possible. During various phases of movements, the tendons are exposed not only to longitudinal but also to transversal and rotational forces. In addition, they must be prepared to withstand direct contusions and pressures. The above-described three-dimensional internal structure of the fibers forms a buffer medium against forces of various directions, thus preventing damage and disconnection of the fibers.

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3-Monoiodothyronamine: the rationale for its action as an endogenous adrenergic-blocking neuromodulator.

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Abstract

The investigations reported here were designed to gain insights into the role of 3-monoiodothyronamine (T1AM) in the brain, where the amine was originally identified and characterized. Extensive deiodinase studies indicated that T1AM was derived from the T4 metabolite, reverse triiodothyronine (revT3), while functional studies provided well-confirmed evidence that T1AM has strong adrenergic-blocking effects. Because a state of adrenergic overactivity prevails when triiodothyronine (T3) concentrations become excessive, the possibility that T3's metabolic partner, revT3, might give rise to an antagonist of those T3 actions was thought to be reasonable. All T1AM studies thus far have required use of pharmacological doses. Therefore we considered that choosing a physiological site of action was a priority and focused on the locus coeruleus (LC), the major noradrenergic control center in the brain. Site-directed injections of T1AM into the LC elicited a significant, dose-dependent neuronal firing rate change in a subset of adrenergic neurons with an EC(50)=2.7 microM, a dose well within the physiological range. Further evidence for its physiological actions came from autoradiographic images obtained following intravenous

carrier-free (125)I-labeled T1AM injection. These showed that the amine bound with high affinity to the LC and to other selected brain nuclei, each of which is both an LC target and a known T3 binding site. This new evidence points to a physiological role for T1AM as an endogenous adrenergic-blocking neuromodulator in the central noradrenergic system.

Thyroid. 2008 Feb;18(2):157-65. doi: 10.1089/thy.2007.0252.

Thyroid-adrenergic interactions: physiological and clinical implications.

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Abstract

The sympathoadrenal system, including the sympathetic nervous system and the adrenal medulla, interacts with thyroid hormone (TH) at various levels. Both systems are evolutionary old and regulate independent functions, playing probably independent roles in poikilothermic species. With the advent of homeothermy, TH acquired a new role, which is to stimulate thermogenic mechanisms and synergize with the sympathoadrenal system to produce heat and maintain body temperature. An important part of this new function is mediated through coordinated and, most of the time, synergistic interactions with the sympathoadrenal system. Catecholamines can in turn activate TH in a tissue-specific manner, most notably in brown adipose tissue. Such interactions are of great adaptive value in cold adaptation and in states needing high-energy output. Conversely, in states of emergency where energy demand should be reduced, such as disease and starvation, both systems are turned down. In pathological states, where one of the systems is fixed at a high or a low level, coordination is lost with disruption of the physiology and development of symptoms. Exaggerated responses to catecholamines dominate the manifestations of thyrotoxicosis, while hypothyroidism is characterized by a narrowing of adaptive responses (e.g., thermogenic, cardiovascular, and lipolytic). Finally, emerging results suggest the possibility that disrupted interactions between the two systems contribute to explain metabolic variability, for example, fuel efficiency, energy expenditure, and lipolytic responses.

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Central effects of thyronamines on glucose metabolism in rats.

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Abstract

Thyronamines are naturally occurring, chemical relatives of thyroid hormone. Systemic administration of synthetic 3-iodothyronamine (T(1)AM) and - to a lesser extent - thyronamine (T(0)AM), leads to acute bradycardia, hypothermia, decreased metabolic rate, and hyperglycemia. This profile led us to hypothesize that the central nervous system is among the principal targets of thyronamines. We investigated whether a low dose i.c.v. infusion of synthetic thyronamines recapitulates the changes in glucose metabolism that occur following i.p. thyronamine administration. Plasma glucose, glucoregulatory hormones, and endogenous glucose production (EGP) using stable isotope dilution were monitored in rats before and 120 min after an i.p. (50 mg/kg) or i.c.v. (0.5 mg/kg) bolus infusion of T(1)AM, T(0)AM, or vehicle. To identify the peripheral effects of centrally administered thyronamines, drug-naive rats were also infused intravenously with low dose (0.5 mg/kg) thyronamines. Systemic T(1)AM rapidly increased EGP and plasma glucose, increased plasma glucagon, and corticosterone, but failed to change plasma insulin. Compared with i.p.-administered T(1)AM, a 100-fold lower dose administered centrally induced a more pronounced acute EGP increase and hyperglucagonemia while plasma insulin tended to decrease. Both systemic and central infusions of T(0)AM caused smaller increases in EGP, plasma glucose, and glucagon compared with T(1)AM. Neither T(1)AM nor T(0)AM influenced any of these parameters upon low dose i.v. administration. We conclude that central administration of low-dose thyronamines suffices to induce the acute alterations in glucoregulatory hormones and glucose metabolism following systemic thyronamine infusion. Our data indicate that thyronamines can act centrally to modulate glucose metabolism.

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