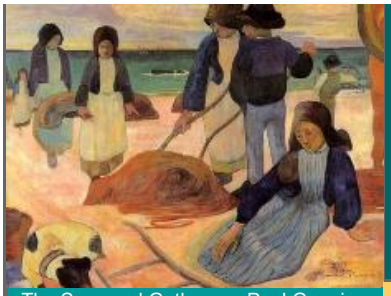

The Seaweed Gatherers, Paul Gaugin

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Multiple Sclerosis

Thyroid hormone and remyelination in adult central nervous system: a lesson from an inflammatory-demyelinating disease.
Calza L, Fernandez M, Giuliani A, D'Intino G, Pirondi S, Sivilia S, Paradisi M, Desordi N, Giardino L.
Brain Res Brain Res Rev. 2005 Apr;48(2):339-46. Epub 2005 Jan 26. Review.

Re-myelination in the adult CNS has been demonstrated in different experimental models of demyelinating diseases. However, there is no clear evidence that re-myelination is effective in multiple sclerosis (MS), the most diffuse demyelinating disease. Moreover, chronic disabilities in MS are believed to be due to remyelination failure and consequent neuron damage and degeneration. Due to the presence of numerous oligodendrocyte precursors inside demyelination plaques, reasons for remyelination failure are unknown. In this paper, we reviewed data from embryonic development and in vitro studies supporting the primary role of thyroid hormone in oligodendrocyte maturation. We also reviewed personal data on the possibility of promoting myelination in chronic experimental allergic encephalomyelitis (EAE), a widely used experimental model of MS, by recruiting progenitors and channeling them into oligodendroglial lineage through the administration of thyroid hormone.

Thyroid function and anti-thyroid antibodies in MS patients screened for interferon treatment. A multicenter study.
Durelli L, Oggero A, Verdun E, Isoardo GL, Barbero P, Bergamasco B, Brossa PC, Ghigo E, Maccario M, Faggiano F; Betaferon Safety Trial (BEST) Study Group.
J Neurol Sci. 2001 Dec 15;193(1):17-22.
[abstract only]

"Interferon beta (IFNB) treatment for multiple sclerosis (MS) has been associated with thyroid disorders (TD), in particular in patients with subclinical TD or anti-thyroid (AT) autoantibodies (autoAb) before starting treatment. TD and AT autoAb frequency was reported increased in MS.

To determine whether MS patients have subclinical thyroid function abnormalities or anti-thyroid autoimmunity predisposing to develop TD, we performed a prospective multicenter screening of thyroid function and autoimmunity in 152 relapsing-remitting (RR) MS patients selected to receive IFNB treatment and in 437 healthy normothyroidal controls. Thyroid-related hormones and anti-thyroid microsomal antigen (anti-TMA) autoAb were tested with sensitive immunoradiometric or chromatographic assays. Cases were stratified for different progressively decreasing or increasing cutoff values of thyroid-stimulating hormone (TSH) (0.3, 0.2, 0.1, 3 and 5 mIU/l), and odds ratios (OR) with 95% confidence intervals (CI) calculated using logistic regression adjusted for gender, age, and anti-TMA autoAb positivity.

The frequency of cases below or above the TSH cutoff values was not significantly different in MS patients and controls, and the risk to have an abnormal TSH level was not significantly increased in MS patients (OR ranging 0.37-0.84; CI, 0.05-3.01), even if anti-TMA autoAb positive (OR ranging 0.35-0.85; CI, 0.04-3.00). Frequencies of subclinical hypothyroidism and of anti-TMA autoAb positivity were, however, trending higher in MS men (ranging 5-7%) than in controls (3%).

MS patients do not have an increased risk of subtle thyroid function abnormalities, subclinical TD, or anti-TMA autoAb positivity that may predispose to develop thyroid dysfunction during IFNB treatment. The positive trend for subclinical hypothyroidism and anti-TMA autoAb positivity, however, advises a longitudinal study of thyroid function and autoimmunity during IFNB treatment to see whether patients with baseline subclinical thyroid dysfunction develop clinically significant alteration during treatment.

Characterization of myelin basic protein thyroid hormone response element and its function in the context of native and heterologous promoter.
Farsetti A, Desvergne B, Hallenbeck P, Robbins J, Nikodem VM.
J Biol Chem. 1992 Aug 5;267(22):15784-8.

"In this report we have characterized further the myelin basic protein (MBP) gene thyroid hormone response element (TRE) by functional and binding analysis. Mutation and deletion experiments revealed that this TRE, confined to the sequences -184 to -167 of the MBP promoter, is able to function as a classical regulatory element in the context of the native and a heterologous promoter. It is comprised of two regions, containing a motif that is highly conserved among other TREs: AGGACA, arranged as an inverted palindrome. Any mutation within the footprinted region impaired receptor binding and function. Moreover, the deletion of sequences outside of the receptor footprinted region (MBP-TRE-18) resulted in a higher triiodothyronine responsiveness and a concomitant increase in receptor-dependent, hormone-independent repression. Results of transfection assays showed that both receptors alpha and beta elicit indistinguishable triiodothyronine responses when the MBP-TRE functions as a regulator of a heterologous promoter activity. However, a preferential beta receptor transactivation was observed when the MBP-TRE was placed in the context of its native promoter."

Molecular basis of thyroid hormone regulation of myelin basic protein gene expression in rodent brain.
Farsetti A, Mitsuhashi T, Desvergne B, Robbins J, Nikodem VM.
J Biol Chem. 1991 Dec 5;266(34):23226-32. Erratum in: J Biol Chem 1992 Aug 25;267(24):17478.

Regulation of myelin basic protein (MBP) gene expression by thyroid hormone has been investigated in rodent brain. Quantitation of the 4 major alternatively spliced transcripts by RNase protection assay showed that the individual mRNAs, corresponding to MBP isoforms 21.5, 18.5, 17, and 14 kDa, were decreased from 2- to 17-fold at all ages studied (4-60 days) in hypothyroid animals when compared to euthyroid, but the timing of onset of expression was not altered. MBP mRNA was also reduced in young adult rats thyroidectomized at the age of 5-6 weeks and was restored to normal by thyroxine administration. Nuclear run-off assays showed that the rate of MBP gene transcription is dependent on thyroid state. Co-transfection of MBP (-256/+1)-chloramphenicol acetyltransferase chimeric gene with a plasmid expressing thyroid hormone receptor alpha, and in

the presence of 3,5,3'-triiodothyronine, into NIH3T3 or NG108-15, increased chloramphenicol acetyltransferase expression 4-fold. Using a footprinting technique and Spodoptera frugiperda 9 (Sf9) nuclear extract infected with baculovirus expressing TR alpha, we have identified a single DNA-binding site (-186/-163) for the receptor. A part of this region contains the AGGACA sequence found in thyroid hormone-responsive elements of other 3,5,3'-triiodothyronine-regulated genes. Our finding of a specific hormone-receptor interaction with the MBP promoter region is the first direct demonstration of a thyroid hormone-responsive element in a brain-specific gene.

The iodine-selenium connection: its possible roles in intelligence, cretinism, sudden infant death syndrome, breast cancer and multiple sclerosis.
Foster HD.
Med Hypotheses. 1993 Jan;40(1):61-5. Review.

Several diseases and disorders display spatial patterns that suggest the involvement of both selenium and iodine deficiencies, or excesses, in their etiologies. It is suggested that many of these similarities in geographical distribution occur because both elements influence thyroid hormone metabolism.

Disease family trees: the possible roles of iodine in goitre, cretinism, multiple sclerosis, amyotrophic lateral sclerosis, Alzheimer's and Parkinson's diseases and cancers of the thyroid, nervous system and skin.
Foster HD.
Med Hypotheses. 1987 Nov;24(3):249-63. Review.
[abstract only]

Geographical distribution patterns of incidence and mortality for a wide variety of diseases display strong positive and negative correlations when analyzed statistically. It is argued that these relationships do not occur by chance, but reflect the causal role of surpluses and/or deficiencies of various bulk and trace elements. This concept is explored for one such "disease family tree", that of iodine. Deficiencies of this essential trace element appear to be associated with many diseases, or birth defects, including goitre, cretinism, multiple sclerosis, amyotrophic lateral sclerosis and cancer of the thyroid and nervous system. Although the evidence is weaker, iodine deficiency may also be implicated in Alzheimer's and Parkinson's diseases. In contrast, too much iodine may be linked to elevated mortality from cancer of the skin and melanoma. Rat studies indicate that iodine deficiencies can cause reduced brain weight, limited myelin formation, retarded neuronal maturation, a lowering of the production of various enzymes and slowing of the rates of protein and R.N.A. synthesis. Similar processes appear to occur in many of the diseases identified above.

Association of MS with thyroid disorders.
Karni A, Abramsky O.
Neurology. 1999 Sep 11;53(4):883-5.
[abstract only]

A controlled prospective study was conducted to determine whether thyroid disorders are present with increased frequency in patients with MS. We found that thyroid disorders were at least three times more common in women with MS than in female controls. This was accounted for mainly by the prevalence of hypothyroidism among the female MS patients. Because hypothyroidism is usually due to Hashimoto's thyroiditis, its association with MS may support the hypothesis of autoimmune pathogenesis for MS. Our findings might have therapeutic implications because interferon treatment can induce antithyroid antibodies and thyroiditis.

Myelin basic protein immunoreactivity in the internal capsule of neonates from rats on a low iodine intake or on methylmercaptoimidazole (MMI).
Martinez-Galan JR, Pedraza P, Santacana M, Escobar del Rey F, Morreale de Escobar G, Ruiz-Marcos A.
Brain Res Dev Brain Res. 1997 Jul 18;101(1-2):249-56.
[abstract only]

"Rats fed on low iodine diets (LIDs) result in a normal circulating level of triiodothyronine (T3), a low level of thyroxine (T4) and an elevated thyroid-stimulating hormone (TSH). These changes are similar to those observed in habitants who live in iodine-deficient areas and different from those observed when the hypothyroidism is produced by goitrogens. To study the effects of LID or goitrogens on the myelin basic protein (MBP) immunoreactivity (MBP-ir) during the myelination of the internal capsule, one group of experimental female rats was fed on an LID, and another group received a standard laboratory diet with methylmercaptoimidazole (MMI) added in the drinking water. Animals fed on a standard laboratory diet and animals fed on an LID supplemented with KI were used as controls. At P10, the MMI treatment has produced a more marked decrease in the surface density of MBP-ir processes with respect to controls than that produced in the LID animals. This decrease was correlated with the cerebral concentrations of triiodothyronine (T3) we found. During the postnatal development, a recovery in the levels of the surface density with respect to controls was observed in both experimental groups. The recovery occurred by P20 in the LID group and by P32 in the MMI rats.

Prevalence of autoimmune thyroiditis and non-immune thyroid disease in multiple sclerosis.
Niederwieser G, Buchinger W, Bonelli RM, Berghold A, Reisecker F, Koltringer P, Archelos JJ.
J Neurol. 2003 Jun;250(6):672-5.
[abstract only]

"Since multiple sclerosis (MS) and autoimmune thyroiditis (AIT) are presumed to be of autoimmune origin the correlation of these two diseases is of special interest. The aim of this study was to determine whether there are differences in the prevalence of thyroid disease with special emphasis on AIT compared with MS and normal subjects and whether the presence of thyroid disease correlates with disability, disease course, age, and disease duration. 353 consecutive patients with clinically definite MS, without interferon-beta treatment and 308 patients with low back pain or headache were extensively examined for the presence of non-immune or autoimmune thyroid disease. We found a significantly higher prevalence of AIT in male MS patients (9.4 %) than in male controls (1.9 %; p = 0.03). The prevalence of AIT in female MS patients (8.7 %) did not differ from female controls (9.2 %). Hypothyroidism, caused by AIT in almost all cases, showed a tendency to be more severe and more often present in patients with MS. There was no association between relapsing-remitting and secondary progressive disease course of MS and the prevalence of AIT. MS patients with AIT were significantly older but did not differ in disease duration and expanded disability status scale (EDSS). Further studies are warranted, to see if there is a difference in sex-hormone levels between MS patients with and without AIT and healthy controls. Longitudinal studies comparing MS patients with or without AIT could show whether there is an influence of AIT on the disease course or progression.