How to Contact Us

Services Dr. Lowe Offers Patients

Evaluation Forms

How to Prepare for Your Metabolic Evaluation

How to Submit Questions

General Information

News

Archived E-mail Newsletters

Publications

Patient-to-Patient Jackie Yellin

About Dr. Lowe

Fibromyalgia Research Foundation

In Memoriam

Links to Other Websites

Myofascial Pain

Nutrition

Testimonials

Theoretical Papers

! Mutations in the John C. Lowe, MA, DC, Malford E. Cullum, PhD, Lloyd H. Graf, Jr, PhD, and Jackie Yellin, BA: *Medical Hypotheses*, 48(2):125-135, 1997.

Abstract. Fibromyalgia, a chronic condition of widespread pain, stiffness, and fatigue, has proven unresponsive to drugs the use of which is based on the "serotonin deficiency hypothesis." An alternate hypothesis, failed transcription regulation by thyroid hormone, can explain the serotonin deficiency and other objective findings and symptoms of euthyroid fibromyalgia. Virtually every feature of fibromyalgia corresponds to signs or symptoms associated with failed transcription regulation by thyroid hormone. In hypothyroid fibromyalgia, failed transcription regulation would result from thyroid hormone deficiency. In euthyroid fibromyalgia, failed transcription regulation may result from low affinity thyroid hormone receptors coded by a mutated c-erbA gene, yielding partial peripheral resistance to thyroid hormone. The hypothesis of this paper is that in euthyroid fibromyalgia, a mutant c-erbA gene (or alternately, the c-erbA alpha1 gene) results in low affinity thyroid hormone receptors that prevent normal thyroid hormone regulation of transcription. As in hypothyroidism, this would cause a shift toward alpha-adrenergic dominance and increases in both cAMP phosphodiesterase and inhibitory Gi proteins. The result would be tissue specific hypothyroid-like symptoms despite normal circulating thyroid hormone levels. (A complete copy of this article is available through AOL's Medline service, or through your local medical library.)

! Why is substance P high in fibromyalgia? Jackie Yellin, BA: *Clinical Bulletin of Myofascial Therapy*, 2(2/3):23-30, 1997.

Abstract. This paper proposes a possible etiology for the increased levels of substance P in the cerebrospinal fluid of fibromyalgia patients. Inadequate regulation of gene transcription by thyroid hormone is the most plausible explanation. Thyroid hormone regulates substance P in discrete nuclei of the brain, in the anterior pituitary, in the lumbar spinal cord, and in the dorsal root ganglia. Most significantly, however, thyroid hormone directly regulates transcription of the preprotachykinin gene, which codes for preprotachykinin-A (the precursor of substance P) and the substance P receptor. Studies confirm the negative regulation of substance P by thyroid hormone: increasing the availability of thyroid hormone decreases levels of substance P; decreasing thyroid hormone increases levels of substance P. Inadequate regulation of gene transcription by thyroid hormone could not only account for high substance P levels, but for all other objective findings and associated symptoms in fibromyalgia. The fact that thyroid hormone negatively regulates substance P, coupled with the finding of a high incidence of hypothyroidism in fibromyalgia patients, should prompt investigation of the possible role of inadequate gene regulation by thyroid hormone in fibromyalgia patients with high substance P levels.

The Metabolic Treatment of Fibromyalgia
by Dr. John C. Lowe
Readers' Comments

! Fibromyalgia & Thyroid Disease. John C. Lowe, MA, DC et al.: Presented and discussed in Grenoble, France, May 6 (conference of the French Fibromyalgia Association of R 間 ion Rh 魅 e-Alpes) and in Toulon, France on May 11 (at the Centre Hospitalier Intercommunal), 2000. Published: Lowe, J. C. et al.: Thyroid disease and fibromyalgia syndrome. *Lyon M 閨 iterran 閑 M 閨 ical: M 閨 ecine du Sud-Est.*, 36(1):15-17, 2000.

[Full text of paper.]

Fibromyalgia & Thyroid Disease

Dr. John C. Lowe et al.

The clinical features of fibromyalgia syndrome (FMS) and hypothyroidism are virtually the same (1,2,3,4,5,6,7,8,9,10). The most common symptoms of FMS are also common symptoms of hypothyroidism, and the objective abnormalities of FMS are also objective abnormalities of hypothyroidism. The symptoms and objective abnormalities of hypothyroidism are mediated by inadequate thyroid hormone regulation of cell function. Inadequate thyroid hormone regulation also plausibly mediates the documented features of FMS (11).

Hypothyroidism in FMS

Primary Hypothyroidism. The estimated incidence of hypothyroidism in FMS is higher than in the general public. The reported incidence of primary hypothyroidism in the general non-elderly USA population varies between 1% (12) and 5% (13). Laboratory thyroid function testing suggests that the incidence of primary hypothyroidism in FMS is 10% to 13% (14, 15, 16, 17, 18).

Anti-thyroid Antibodies. Aarflot and Bruusgaard measured thyroid microsomal antibodies in 737 men and 771 women who ranged in age from 40-to-42 (19). Subjects with chronic widespread musculoskeletal complaints had a significantly higher incidence of antibodies than did subjects without such complaints (16.0% versus 7.3%, $p<0.01$). The prevalence of antibodies was significantly higher in women than men (20.4% versus 11.6%, $p = 0.02$). It is noteworthy, however, that laboratory thyroid function test results did not differ significantly between the two groups. The investigators wrote that their results suggest that patients with microsomal thyroid antibodies may have symptoms due to subnormal thyroid hormone regulation of cell function before thyroid gland dysfunction is detectable by tests of thyroid hormone and TSH levels. The researchers implied that many patients diagnosed with FMS may in fact have chronic, widespread pain due to impaired thyroid gland function revealed only by increased titers of thyroid microsomal antibodies. If this is true, then the incidence of primary hypothyroidism among FMS patients may be higher than the 10% to 13% suggested by measures of TSH and thyroid hormone levels.

Central Hypothyroidism. The incidence of central hypothyroidism, involving hypothalamic or pituitary dysfunction, in the USA population at large is about 0.00021% (12). Our research group has found that of 92 sequential unselected FMS patients, 40 patients (43.5%) had laboratory test results consistent with central hypothyroidism (16, 18). Other researchers have also reported high incidences of test results consistent with central hypothyroidism (20,21).

Thus, the incidence of primary hypothyroidism among FMS patients may be 2 to 10 or more times higher than in the USA population at large. The incidence of possible central hypothyroidism, however, may be 250,000 times higher. If we trust that thyroid function test results are reliable, we are compelled to reach a conclusion: If 10% of FMS patients have primary hypothyroidism, and 44% have central hypothyroidism, the total percentage of FMS patients with hypothyroidism is 54%.

Thyroid Hormone Resistance

Many researchers and clinicians consider the term "thyroid disease" to include only pathological processes that occur 1) within the thyroid gland itself, or 2) in other tissues, such as the pituitary gland, and indirectly result in subnormal function of the thyroid

gland. However, this definition may be too narrow. In 1967, Refetoff et al. provided convincing evidence of partial cellular resistance to thyroid hormone in humans (22). Since then, a great volume of studies of human thyroid hormone resistance has accumulated. Also, mutations in the c-erbA gene on chromosome 3 (which codes for the T3-receptor) have been shown to be the underlying mechanisms of general resistance to thyroid hormone (23). (The mechanisms of resistance in most afflicted patients remain unknown.) In some thyroidology textbooks, thyroid hormone resistance is grouped under "Special Topics in Thyroidology." However, it can be argued that thyroid hormone resistance should be classified as a subset of thyroid disease. As in central hypothyroidism, which is classed as a thyroid disease, thyroid gland function is indirectly altered in two classifications of thyroid hormone resistance. Also as in primary and central hypothyroidism, patients with symptoms and signs caused by thyroid hormone resistance can be effectively treated with thyroid hormone (albeit in higher than physiologic dosages, called "supraphysiologic" dosages).

Thyroid Hormone Resistance and FMS. As far back as the late 1980s, I (JCL) was puzzled as to why euthyroid FMS patients (those with normal thyroid test results) had identically the same hypothyroid-like symptoms and signs as did hypothyroid FMS patients. In searching for an answer, I came into communication with thyroid hormone resistance researchers. One of these, Steve Usala, had established a link between the c-erbA gene and thyroid hormone resistance (24). He was also first to discover a mutation in the gene (25). (More than 100 different mutations in the gene have now been discovered (11).) Based on communication with Usala and other thyroid hormone resistance researchers, in 1990, my colleagues and I treated 77 euthyroid female FMS patients with T3 (as part of comprehensive metabolic treatment).

This treatment was based on our hypothesis that the patients had partial cellular resistance to thyroid hormone (26). Of the 77 patients, 19 (25%) did not feel that T3 had improved their status. They were withdrawn from use of the hormone. The remaining 58 patients (75%) reported that their symptoms were improved to varying degrees. For the group, the difference between pre- and post-treatment algometer scores (mean of the pressure/pain threshold of 18 tender points) was highly significant (p:< 0.0005). The mean pressure/pain threshold of the 18 tender point sites was significantly higher (improved) after T3 treatment. Effective dosages of T3 ranged from 75 ¿g. to 150 ¿g.

Most patients improved with dosages between 81.25 ¿g. and 100 ¿g. (Normal replacement dosages were reported to be from 25-to-75 ¿g.) Since that early open trial, we have continued to treat euthyroid FMS patients on the assumption that they have thyroid hormone resistance. We find that approximately 75% of euthyroid FMS patients markedly improve or completely recover when treated with what we term "metabolic rehabilitation." The treatment involves the use of T3, exercise to tolerance, wholesome diet, nutritional supplements, physical treatment, and cessation of the use of metabolism-impeding medications.

Most euthyroid patients improve only with supraphysiologic dosages of T3. We are convinced that the patients who improve or recover with supraphysiologic dosages of T3 have cellular resistance to thyroid hormone. We conclude that a patient has thyroid hormone resistance when four criteria are met. The patient:

(1) is euthyroid before beginning the use of T3, according to thyroid function test results, including a TRH stimulation test;

(2) markedly improves or completely recovers from hypothyroid-like FMS symptoms and signs with supraphysiologic dosages of T3;

(3) after beginning T3 therapy has an extremely high free T3 blood level;

(4) has no evidence of tissue thyrotoxicosis due to the high free T3 level, according to the results of serial ECGs, serum and urine biochemical tests, and bone densitometry.

Most of our euthyroid patients who improve or recover with metabolic rehabilitation involving T3 therapy meet these four criteria. Clearly, this set of findings in many treated euthyroid FMS patients shows that they meet Refetoff ¿ definition of thyroid hormone resistance: "reduced responsiveness of target tissues to concentrations of thyroid

hormone that under normal conditions would be excessive" (23). According to the four criteria, we have documented the presence of thyroid hormone resistance in FMS patients in several double-blind, placebo-controlled, crossover studies (27, 28, 31). Also, in a case-control study, we found that the results of the treatment lasted long term (29). Throughout a 1-to-5 year follow-up period, 10 hypothyroid FMS patients maintained their improvement compared to untreated FMS matched control patients. Also, 10 euthyroid FMS patients treated with T3 maintained their improvement compared to control patients.

Criticisms

Eisinger (rheumatologist) and Fontaine and Rinaldi (thyroid specialists) have given several criticisms of the hypothesis we present here (30). We agree with most of the criticisms. For example, we know that a small amount of the available evidence contradicts the hypothesis. Despite this, the hypothesis is supported by far more of the available evidence than is any competing hypothesis of the etiology of FMS. Also, rigorous logical analyses show that the hypothesis is the most useful at this time for stimulating further fruitful theoretical and experimental exploration of FMS.

Eisinger, Fontaine, and Rinaldi also argued that the hypothesis applies only to a subgroup of FMS patients. We maintain that the subgroup is large 梒 lose to 90%. We agree with them, however, that patients should be treated with precaution. We also agree with an astute observation of theirs: that when the peripheral cellular effects of thyroid hormone can be normalized by agents such as selenium (which may increase the monodeiodination of T4), this therapy is preferable to the use of exogenous thyroid hormone. (The American FMS/thyroid researcher Richard Garrison has made a similar argument.) We should rigorously study the treatment of FMS patients with agents such as thiol and selenium to learn whether some of the patients benefit more from these agents than from the use of T3. Even when patients do benefit from such agents, however, the benefits are mediated by an improvement in thyroid hormone regulation of cell function. This outcome further supports the hypothesis that in the involved patients, inadequate thyroid hormone regulation of cell function underlies their FMS.

Conclusions

If cellular resistance to thyroid hormone is accepted as a subset of thyroid disease not directly involving the thyroid gland, then our findings suggest that most FMS patients have thyroid disease. About 10% have laboratory test results consistent with primary hypothyroidism, and about 45% have results consistent with central hypothyroidism. This is a total of 55% of FMS patients who may have hypothyroidism.

Of the remaining 45% who have test results consistent with euthyroidism, 75% on average improve or recover when treated on the assumption that they have thyroid hormone resistance. This 75% is about 34% of our total sample of FMS patients. For a total percentage of FMS patients with possible thyroid disease, we can add this 34% of patients with thyroid hormone resistance (according to the four post-treatment criteria) to the 55% of hypothyroid patients (according to thyroid function test results). The result is 89% of FMS patients with putative thyroid disease. (See Table 1.)

This estimate is consistent with previous findings such as glycolysis abnormalities and T3-induced improvement in FMS patients with the polymyalgia-hypothyroid intractability syndrome described by Eisinger (11,14). In fact, as I (JCL) recently argued (11), virtually every symptom and abnormal finding in FMS is plausibly explained by inadequate thyroid hormone regulation. This proposed mechanism is unique in this respect.

Table 1. Percentage of FMS patients with thyroid disease.

Class of Thyroid Disease	% of Patients
Primary hypothyroid	10%
Central hypothyroid	45%
Thyroid hormone resistant	34%
Total % with thyroid disease	*89%*

The remaining 11% of FMS patients also have symptoms and signs that resemble those of hypothyroidism. Our conjecture is that these patients' symptoms and signs result from pathophysiological processes not related directly to thyroid hormone. However, we believe the pathophysiological processes in these patients impede metabolism in a set of tissues that generate symptoms and signs resembling those of hypothyroidism or thyroid hormone resistance.

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