Psychoneuroimmunoendocrinology Review and Commentary
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Psychoneuroimmunoendocrinology describes the unity of mental, neurological, hormonal, and immunological functions, addressing the impact of cognitive images of the mind (whatever its elusive definition) on the central nervous, endocrine, and immune systems. It encompasses biofeedback and voluntary controls, impacts on physiology of thought and belief, past/present stress, placebos, social relationships, and "energy medicine." This column highlights clinical applications of cogent studies from these arenas of holistic medicine in the new millennium.

Stress Gastritis and Thyroid Hormone
The aim of this study was to investigate the effect of low circulating thyroid hormone levels on the development of acute stress gastritis in rats. Sixty adult Sprague-Dawley rats were divided into three groups: a stressed group; a thyroidectomized + stressed group; and a thyroidectomized + T3 + stressed group. Damage to the gastric mucosa was studied using millimetric acetate papers on photographs enlarged 3.5 times, and the number and the size of the lesions was recorded. The acute stress gastritis score in the stress + surgically thyroidectomized rats was 44 vs. 16 in rats that were stressed but not thyroidecomized vs. 10 in the thyroidectomized + T3 + stressed group (p< 0.001 for both comparisons). Low circulating thyroid hormone levels in rats increased the development of stress gastritis. This effect appeared to be prevented by thyroid hormone T3 replacement therapy.


COMMENT: It is well established that acute stress has the propensity for causing acute gastritis. Intensivists in hospital care take steps to prevent and treat this issue in highly stressed, acutely ill ICU patients. The result of this rat study implies that low circulating thyroid hormone levels worsened the development of acute gastric changes associated with stress and that replacement administration of T3 in the face of this deficiency attenuated the downside effects. This would imply that hypothyroid patients would need extra caution in dealing with potential acute stress gastritis.

Shift Work Stress and Autoimmune Hypothyroidism
The immune system and the neuroendocrine system machinery modulate each other, including the effects of stress from life events and interpersonal conflicts, promoting the synthesis of proinflammatory cytokines, the overproduction of which influences behavior. In addition, the balance of systemic and local pro-inflammatory cytokines to systemic and local anti-inflammatory cytokines is impaired to such an extent that, in genetically predisposed individuals, this aberrancy may lead to autoimmune diseases. Occupational stress likely influences their onset. For example, subclinical autoimmune hypothyroidism was identified in numerous shift-workers of an Italian hospital. Such a threat impacted the policy of health surveillance of the workers. This highlights the need for further studies on the relationship between occupational stress, autoimmunity, and hypothyroidism.


COMMENT: Shift work (rotating shifts) in nurses, police, and fire personnel is known to induce chronic stress. The authors conclude that this aspect of occupational stress is closely tied to autoimmunity and hypothyroidism. Indeed, production of antithyroid antibodies is a major antecedent in hypothyroidism. See autoimmune thyroid disease (AITD) below.

Stress and Autoimmune Thyroid Diseases
Autoimmune thyroid diseases (AITD) are by far the most common autoimmune disorders, with prevalence in Western countries exceeding five percent of the general population. In a large majority of individual cases, the clinical impact of AITD is not severe, but the widespread diffusion of these diseases renders them a significant health problem. AITD are heterogeneous in their clinical presentation, the two main forms being autoimmune (Hashimoto’s) thyroiditis (AT) and Graves’ disease (GD). They probably share, at least in part, a common genetic background. They are two distinct diseases, both in their clinical presentation and their pathophysiology. AT causes structural thyroid
damage via cell-mediated immune destruction of thyroid follicular cells, which results in functional impairment and hypothyroidism; thyroid function impairment may occur after an initial phase of mild thyrotoxicosis due to relatively rapid gland destruction. GD patients have hyperthyroidism, often severe, due to autoantibody-mediated thyrotropin receptor stimulation, with thyroid cell hyperplasia and hyperfunction. The therapy of AITD is mainly the therapy of thyroid dysfunction. AT may be asymptomatic for a long time, and defining its natural history in a single patient may be difficult. In some AITD patients (mainly, but not exclusively, with GD), clinical features such as ophthalmopathy are present.


COMMENT: Stress has been related to autoimmune thyroid diseases, which may present as hypothyroidism or hyperthyroidism (Graves’ Disease). The incidence of Graves’ Disease in Norway increased several-fold during the Nazi occupation in World War II. And new Graves’ patients are 6.3-fold more likely to have a prior year of high stress scores (Winsa B et al. Lancet. 1991; 338:1475). It is not a leap to think that all AITD may be in part triggered by stress.

Post-Operative “Euthyroid Sick Syndrome”

Hypothyroidism and hyperthyroidism are conditions commonly present in adults, leading to neurological symptoms affecting the central and peripheral nervous systems and to neurocognitive impairment. The so-called “euthyroid sick syndrome,” characterized by reduced serum T3 and T4 concentrations without increased serum TSH secretion, occurs within hours after major surgery. After the stress of surgery, elderly patients often exhibit a transient, reversible state of cognitive alterations. This delirium occurs in 10-26% of general medical patients over 65, and it is associated with a significant increase in morbidity and mortality. Modifications in thyroid hormone functioning may take place as a consequence of psycho-physical stress caused by surgery and probably as a consequence of reduced conversion of T4 into T3 by the liver highly engaged in metabolizing anesthetic drugs. Therefore, post-surgery modifications of thyroid hormones might play a role in the pathogenesis of postoperative cognitive dysfunction. Matraca F, Fodale V. Thyroid function, Alzheimer’s disease and postoperative cognitive dysfunction: a tale of dangerous liaisons. J Alzheimer’s Dis. 2008; 14:95.

COMMENT: There are other postulated mechanisms explaining the reduced T4 and T3 after the stress of surgery (see below). Post-surgical patients might benefit from brief supplementation with thyroxin for several days.

Stress, Cytokines, and the Thyroid

Cytokine release may be implicated in thyroid hormone changes during and following surgical stress. In 36 adult patients (20 men and 16 women, mean age 68.5) undergoing elective major abdominal operations, TNF-α, interleukin-6 (IL-6), interleukin-8 (IL-8), and interleukin-10 (IL-10), and TSH, free T4, and T3 were checked before surgery, immediately postoperatively, and on the first and second postoperative days. TNF-α, IL-6, and IL-8 peaked on post-op day 1, and IL-10 peaked immediately postoperatively. After surgery, 14/36 patients had low T3 levels. Significant negative correlations were noted among TNF-α, IL-6, and IL-8 against free T3 and free T4. Cytokines are responsible, at least in part, for non-thyroidal illness following major operations. Ilies I, Tzanela M, Manou I, et al. Thyroid function changes and cytokine alterations following major surgery. Neuroimmunomodulation. 2007; 14:243

COMMENT: The stress of surgery clearly quickly reduces the production of thyroid hormone. The mechanisms are not clearly and completely understood. This study implies that these acute changes may be modulated through the release of a number of cytokines.

Subclinical Hypothyroidism and Arterial Function

Subclinical hypothyroidism (SCH) is associated with increased risk of cardiac disease through several possible mechanisms. This six-month controlled observational study used pulse wave analysis and tissue Doppler echocardiography to evaluate 19 women SCH patients with increased TSH, normal free T4, and no cardiovascular disease (mean age 49), compared to ten healthy women controls (mean age 50). Incremental doses of L-thyroxin were used. Baseline augmentation gradient for vascular stiffness was 10.8 mmHg in SCH subjects vs. 8.0 in controls (2p<0.05). The gradient fell to 8.8 mm Hg with incremental thyroxin treatment. The corrected augmentation index was 26.7 vs. 18.8% (p<0.02), respectively, falling to 19.7 (p<0.001) after treatment. Arterial stiffness was increased in SCH and improved with L-thyroxin. Owen PI, Rajiv C, Vinereanu D, et al. Subclinical hypothyroidism, arterial stiffness, and myocardial reserve. J Clin Endocrinol Metab. 2006; 91:2126

COMMENT: I include this study to point out that the effects of hypothyroidism, even at a “subclinical” level, involve every conceivable bodily function. This reduced arterial compliance in these women may be one mechanism by which heart disease is observed to be more common in hypothyroidism.

Subclinical Hypothyroidism, Exercise, and Reactive Oxygen Species

Intensive muscular exercise promotes the production of reactive oxygen species (ROS) in the working muscles and can impair athletic performance, particularly in conjunction with inadequate recovery. Mammals are protected against oxygen toxicity by a system of ROS scavengers composed of enzymatic and non-enzymatic components. Antioxidant supplementation has recently been considered as a means to diminish or prevent damage from ROS, but the specific antioxidant requirements of athletes are not known. Since normal thyroid function is essential for athletic performance, thyroid supplementation should be undertaken in cases where there is any sign of thyroid dysfunction “of unknown etiology.” Hyperthyroidism and hypothyroidism have been
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associated with increased production of ROS as well as related inflammatory response and myopathy.

COMMENT: The authors believe that increased populations of reactive oxygen species are associated with and possibly caused by aberrations of thyroid functions. This is just one additional reason among many to have a high index of suspicion for this common condition of subclinical hypothyroidism.

FT3, rT3, Age, and Energy Intake
Both fasting and hypercaloric diets induce low triiodothyronine levels that resemble the "Euthyroid Sick Syndrome." In 440 randomly selected subjects, age 65-85, 11 had low Free T3 levels and 21 had elevated rT3 levels. The latter had lower energy and fat intakes. With age, rT3 clearly increased and FT3 decreased, even within the normal range and in spite of adequate caloric intake. There was also a correlation with FT3 and poorer health status. Greater age and lower energy intakes were the best predictors of increased rT3.

COMMENT: "Greater age and lower energy intakes" predicted increased rT3. Or did increased rT3 predict lower energy intakes? I think the answer is not yet known. And the meaning and significance of increasing rT3 with advancing age is not yet clear. Is rT3 a reciprocal of FT3? Again, I think the complete answer is not known. The present clinical answers would be to eat appropriately, manage stress, and don't grow old!

Hypothermia Stress and Reverse T3
In 16 armed forces men, exposure to cold for 76 days increased rT3 levels 30% from a mean of 27 to 35 pg/ml (p< .006) and decreased free T3 levels 20% from 2.82 to 2.23 pg/ml (NS). T4 and TSH were not correlated.
McCormack PD, et al. Increase in rT3 serum level is observed during extended Alaskan field operations of naval personnel. Alaska Med. 1996; 38:89.

COMMENT: Here again is evidence that stress — in this instance, physical stress — alters T3 function. A simple explanation is not justified, as evidenced by the study below.

Reverse T3
This study purported to show that reverse triiodothyronine (rT3) is synthesized in the brain and choroid plexus and is prevented by the blood brain barrier from entering peripheral circulation. It may exert important brain-specific and site-specific functional effects.

COMMENT: Observers of thyroid function seem to believe that we know all about the function of this endocrine gland. We obviously do not, as evidenced here. In managing patients with clinical symptoms of aberrant thyroid function, the clinical picture should rank of equal importance with laboratory values. I have treated countless hypothyroid patients who responded to mildly increased supplemental doses of Armour thyroid or a combination of Synthroid (T4) and Cytomel (T3) which would not have been warranted by laboratory results. At some future point, we may better understand the complexities and better serve our patients with symptoms of aberrant thyroid hormone function.

Thyrotropin and Post-Surgical Stress
In ten patients followed for six days after surgery, operative trauma was associated in all patients with significant decreases in serum total and free T3 and a significant increase in serum reverse T3 (rT3) levels, with no variations in serum total and free T4 concentrations. Marked rise in serum cortisol was observed, with higher values at night vs. morning. Serum cortisol and circadian rhythm normalized on the fifth day. AM serum TSH values significantly fell on the first post-op day and returned to normal on the second day. Serum TSH values at night (midnight to 2 AM) were higher than in the morning preoperatively, but the nocturnal surge was abolished from days 1-5 after surgery and was restored to normal only on post-op day 6. Thus, the stress of surgery was associated with a prolonged loss of the nocturnal serum TSH surge. This effect on TSH secretion was more marked than would have been predicted on the basis of serum TSH measurements in the morning alone. An inverse relationship was found between serum cortisol and serum TSH values at night, suggesting that the excessive endogenous cortisol secretion might play a role in the reduced TSH secretion.

COMMENT: All the possible mechanisms by which stress reduces thyroid hormone elaboration have not been elucidated. One emerges from this study. It is possible that stress, through sympathetic neural innervation (see below), may alter triiodothyronine and rT3 production. Again, the practical meaning of an increased rT3 level is not clearly understood, either. It might be possible that stress alters the interrelationship between T3 and rT3, reducing the total metabolic effect.

Sympathetic Innervation of the Thyroid
Fluorescence histochemistry was utilized to study the sympathetic innervation of the thyroids from adult individuals of six different species: mouse, rat, hamster, dog, sheep, and pig. Additionally, thyroids from both very young and very old mice were examined. Thyroidal sympathetic adrenergic nerve terminals were found as single terminals between, and sometimes around, thyroid follicles. Interfollicular terminals were numerous in the thyroids of adult mice, sheep, and hamsters, but fewer in...
the thyroids of adult rats and dogs and even fewer in the porcine thyroid. In contrast to the findings in thyroids from adult mice and rats, several interfollicular terminals were found in thyroids from very young rats, while very few such terminals were detected in the thyroids from very old mice. These observations suggest that there is an interspecies variation in the number of thyroidal interfollicular sympathetic nerve terminals and that, in the rat and the mouse, there is also a variation with age. Since sympathetic activation appears to induce thyroid hormone secretion in mice by a direct action of norepinephrine released from intrathyroidal sympathetic fibers, the recorded variations presumably have functional importance.

COMMENT: The implications from this study for parallel activity in humans are apparent and enormous. Sympathetic activation induced increased thyroid secretion. It follows that an understanding of the profound influence of physical and psychosocial stress on sympathetic neural activation is probably quintessential to fully explicating an enhanced comprehension of thyroid function.

Direct Neural Communication of the Brain to the Thyroid

The sympathetic superior cervical ganglia provide innervation to the thyroid and parathyroid glands through the external carotid nerve. Postsynaptic activation in median eminence nerve endings shortly after superior cervical ganglionectomy was accompanied by a decrease in TSH release. These effects were accompanied by an increase in medial basal hypothalamic Thyrotropin Releasing Hormone (TRH). In thyroid tissue, alpha 1-adrenoceptor inhibition of thyroxin (T4) release was observed during the degeneration phase after ganglionectomy. Thyroid sympathetic nerves also modulate slow phenomena such as compensatory thyroid growth after partial thyroidectomy. In rats subjected to cholinergetic decentralization of the thyroid gland, a decrease of plasma T4 and an increase of plasma TSH, as well as an impaired goitrogenic and thyroid compensatory response, were detectable. The results indicate that cervical autonomic nerves constitute a parallel pathway by which the brain communicates with the thyroid.


COMMENT: In my medical school training, the communication of the hypophysis and pituitary to the thyroid was thought to be exclusively through secretion of thyroid stimulating hormone. There was no mention of neural innervation of thyroid tissue. The sympathetic and parasympathetic branches of the autonomic nervous system are essential to the dissemination of stress messages to body organs. If we are looking for a plausible explanation of how stress alters thyroid function, this demonstrated neural connection might well be the answer.

Dehydroepiandrosterone and Stress

This review presents strong clinical evidence that type A subjects are hyper-responsive to stress and that catecholamines play a pathogenic role in coronary artery disease. The authors postulated that dehydroepiandrosterone (DHEA), as a weak androgen, is inversely correlated with the type A behavior pattern. In 23 chronically stressed men, DHEAS was lower and DHEAS/cortisol ratio also significantly decreased (p<.001) vs. unstressed normal controls. This indicates that during stress there is a shift away from pregnenolone and androgens to glucocorticoids.


COMMENT: The significance of the fall in DHEA and DHEAS is still not yet fully appreciated. The endocrine participation of DHEA as a hormone in its own right has been shown to affect scores of bodily functions. By and by, we shall see through a glass clearly. Stress is clearly inversely correlated with DHEAS levels (Labbate L et al. Psychosomatics. 1995; 36:555).

Adrenal Insufficiency and Stress

Adrenal insufficiency is being diagnosed with increasing frequency in critically ill patients. There is much controversy about its pathophysiology, epidemiology, diagnosis, and treatment. Activation of the hypothalamic-pituitary-adrenal axis with the production of cortisol is a fundamental component of the stress response and is essential for survival of the host, and dysfunction of the HPA axis with decreased glucocorticoid activity is being increasingly recognized in stressed critically ill patients, especially those with sepsis. This condition would best be referred to as "critical illness-related corticosteroid insufficiency." Critical illness-related corticosteroid insufficiency leads to an exaggerated proinflammatory response with increased tissue injury and organ dysfunction.


COMMENT: Critical illness-related corticosteroid insufficiency is common in critically ill patients, particularly those with sepsis. Supplemental corticosteroids may restore the balance between the pro-and anti-inflammatory mediators in patients with severe sepsis, septic shock, and acute respiratory distress syndrome, thus improving the outcome of patients with these conditions. The mechanisms by which the adrenal response is blunted may have some parallels with low thyroid response under stress as discussed above. To be aware of the possibility of both conditions is essential for best clinical care.

Robert Anderson is a retired family physician who has authored several major books: Stress Power!, Wellness Medicine, Clinician's Guide to Holistic Medicine (2001), and The Scientific Basis for Holistic Medicine, (6th edition, 2004), available from American Health Press, holos@charter.net. Anderson founded the American Board of Integrative Holistic Medicine, is a past president of the AHMA and former Assistant Clinical Professor of Family Medicine at the University of Washington, and teaches The Art of Primary Care at Bastyr University.