576 1/02 Rev. 11/03
ANSR–APPLIED NUTRITIONAL SCIENCE REPORTS

Nutritional Management of Stress-Induced Dysfunction

ABSTRACT: *In today's fast-paced society the vast majority of individuals are under a constant barrage of stressors. These stressors are translated by the neuroendocrine system into signals that alter the body's biochemistry to support a "fight or flight" response. While some of these changes may be beneficial to survival in the short term (acute stress), they present an increased risk of various physical and psychological health challenges in the long term (chronic stress). There is no doubt that stress is an inevitable consequence of modern life; fortunately, the downstream damage caused by it is not. The use of natural substances can support normalization of stress-induced biochemical and organ function changes and increase nonspecific resistance to stress. These natural alternatives offer healthcare professionals a safe and effective way to support the health and well-being of their patients through stressful periods, promote healthy aging, and help prevent the vast array of health issues that are associated with chronic activation of the body's stress response.*

Stress can be defined as any perceived physical or psychological change that disrupts an organism's metabolic balance. Surveys and research reports conducted over the past 2 decades reveal that 43% of all adults suffer adverse effects due to stress. In fact, 75% to 90% of all visits to primary care physicians are in some way related to the adverse impact of psychosocial stress. Furthermore, an estimated 1 million workers are absent on an average workday because of stress-related complaints. The market for stress management programs, products, and services has skyrocketed in the past decade and is estimated to currently exceed $11 billion annually.[1] While all age groups are affected by stress, the aging population faces compounded susceptibility to stress-induced disorders because of the accumulation of problems mediated by chronic, long-term stress.[2]

THE HYPOTHALAMIC-PITUITARY-ADRENAL (HPA) AXIS

The central nervous system (CNS) acts as an "antenna" that translates stressors into biochemical signals filtered through the HPA axis (Figure 1). In general terms, a stressor is perceived by the limbic system, which stimulates corticotropin-releasing hormone (CRH) in the hypothalamus. CRH then travels to the pituitary gland where it triggers the release of adrenocorticotropin hormone (ACTH). ACTH, in turn, triggers the production and release of glucocorticoids (GCs), such as cortisol, from the adrenal glands. The hypothalamus also stimulates the adrenal medulla, via the sympathetic nervous system, to release catecholamines, such as epinephrine (adrenaline) and norepinephrine (noradrenaline). GCs and catecholamines induce a variety of behavioral, biochemical, and physiological changes, collectively termed the *stress response*.[2,3] For instance, the release of GCs and catecholamines during stress result in increased alertness, elevations in blood glucose and blood lipids, increased oxidant production, and an increased heart rate. In the acute stress scenario, these induced changes serve to increase the organism's chance of survival.[4]

HYPERACTIVATION OF THE STRESS RESPONSE

Chronic activation of the HPA axis brought on by repeated exposure to stressors can cause organ systems to functionally deteriorate as they constantly attempt to re-establish the internal balance that has been perturbed by the stress response. In addition, hyperactivation of the HPA axis can lead to a net excess of cortisol, causing hypercortisolemia. Over time, hypercortisolemia promotes catabolism (e.g., neuronal atrophy, loss of bone density) and negatively influences system function at multiple levels.[3,5] Research also suggests that aging is associated with changes in the regulation of the HPA system, which result in its hyperactivation and excess GC release.[2,6] Stress-induced hypercortisolemia, as well as the excessive release of catecholamines, may curtail life expectancy by several years via their downstream effects on physiology and organ/system function.[4,7] Chronic stress also impacts the synthesis and activity of aldosterone, thereby influencing sodium and potassium concentrations and extracellular fluid volume.

Research increasingly supports the critical role that stress and stress molecules can play in obesity, diabetes, osteoporosis, hypertension, cardiovascular disease, infectious disease, gastric ulcer, cancer, and gastrointestinal, skin, and neurologic disorders, as well as a host of disorders linked to immune system disturbances. Chronic stress has also been shown to affect behavior in both human and animal models, and has been linked to psychiatric illness such as depression and anxiety in humans.[1,4,5,7-11] The vulnerability of a particular body system to stress varies from one individual to another and is determined by genetic and constitutional make-up and may be influenced by environmental factors.[3] Identifying those with symptoms of HPA hyperactivation may allow for early intervention and the avoidance of stress-related disorders (Figure 1).

Special reference should be made to the effect of chronic stress on cardiovascular health—a primary concern for many patients. Recent studies provide convincing evidence that chronic life

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stress contributes significantly to the pathogenesis of coronary artery disease.[4,7,12,13] Excessive action of fatty acids (released through the catabolic processes of stress) and cortisol causes insulin resistance and increases the hepatic secretion of glucose and very low density lipoproteins (VLDL). Furthermore, cortisol can decrease the uptake of LDL by the liver.[13] Catecholamines influence heart rate, blood pressure, heart rhythm, and many other parameters of cardiovascular function.[3,5,7,8] Clinical consequences of these effects, in the chronic stress scenario, may include myocardial ischemia, arrhythmias, endothelial dysfunction, and the potential for thrombosis.[7] *(For more information on the natural prevention of cardiovascular disease, please refer to the articles "Part I: Cardiovascular Disease Risk Factors and Fundamental Nutrition" and "Policosanol: An Exciting Natural Compound That Lowers Cholesterol and Promotes Cardiovascular Health.")*

FROM HYPERACTIVATION TO HYPOACTIVATION

Interestingly, stress may not only cause HPA axis hyperactivation and the attendant problems mentioned above, but in certain individuals long-term stress can result in just the opposite—a "burnout" or hypoactivation of the stress response. A number of studies now indicate that after long-term exposure to stress, the HPA axis may eventually lose its ability to adapt to stressors, resulting in hypoarousal, the disruption of central regulatory systems (e.g., circadian rhythm), and a net decrease of cortisol output.[3,14-16] Hypocortisolemia is associated with a distinct clinical picture (Figure 1) and may promote an increased vulnerability to autoimmune disorders, inflammation, myocardial infarction, chronic pain, asthma, and allergies.[3,5,15-17] This process may relate to Hans Selye's model of "exhaustion," which states that the ability to adapt to stress is lost because adaptation utilizes bodily resources and taxes the organ systems. Eventually one or more systems may break down, resulting in disease.[11]

According to Heim, et al., potential mechanisms that may lead to hypocortisolemia include: 1.) CRH hypersecretion, leading to the adaptive down-regulation of pituitary CRH receptors; 2.) increased negative feedback sensitivity within the HPA axis; 3.) morphological changes (e.g., adrenal atrophy); and 4.) reduced biosynthesis or depletion of stimulating factors and hormones (e.g., CRH, ACTH, cortisol).[17] In addition, factors such as the nature of the stressor, coping styles, genetics, developmental factors (e.g., early life trauma), and personality styles may be precipitating factors.[17,18]

Under normal conditions, a negative feedback loop maintains the balance of cortisol—CRH is modulated primarily by levels of GCs, but also by levels of ACTH and CRH itself. In addition, CRH is also modulated by neurotransmitter systems within the limbic system, which may include serotonergic, cholinergic, gamma-aminobutyric acid (GABAergic), dopaminergic, and opioid peptide (e.g., morphine, endorphins) systems.[3,5]

It is evident that HPA dysfunction is far-reaching. In fact, HPA dysfunction may also impinge upon the proper function of the metabolic regulator, the thyroid.

THE HYPOTHALAMIC-PITUITARY-THYROID AXIS AND THYROID HORMONE ACTIVITY

The hypothalamus produces thyrotropin releasing hormone (TRH), which stimulates the pituitary gland to release thyroid stimulating hormone (TSH) (Figure 1). TSH then signals the thyroid gland to increase hormone synthesis—this is known as the hypothalamic-pituitary-thyroid (HPT) axis. In response to stimulation by TSH, the thyroid gland primarily produces the thyroid hormone thyroxine (T4). Two other thyroid hormones, triiodothyronine (T3) and reverse T3 (rT3), are largely peripherally produced via enzymatic deiodination (conversion) of T4.[19,20] The metabolically active form of thyroid hormone is T3, and rT3 may act as a competitive inhibitor of T3, serving as a built-in system for downregulation of thyroid hormone activity. It is estimated that more than 70% of T4 is eventually deiodinated in peripheral tissues (largely liver and kidneys) to form T3 or rT3.

Deficient thyroid hormone activity may be due to a lack of stimulation by the pituitary gland, defective hormone synthesis, impaired conversion of T4 to T3, increased levels of rT3, or perhaps poor T3-mediated gene expression, all resulting in a poor biological response.[21,22] Millions of people may suffer from mild hypothyroidism and not know it. In fact, as many as 10% of women may have some degree of deficient thyroid hormone activity.[23]

The Relationship to Stress

Stress may influence the HPT axis at both the primary level of hormone production and through alteration of peripheral hormone metabolism (Figure 1). For instance, CRH causes indirect inhibition of TSH at the pituitary level and high levels of cortisol may be responsible for altered peripheral metabolism of T3 and rT3 observed during stress. For example, research suggests that cortisol has an inhibitory effect on 5'-deiodinase, which converts T4 to T3, while it seems to favor the conversion of T4 to rT3.[19,24,25] Furthermore, rT3 may also inhibit 5'-deiodinase.

The formation of T3 may be more heavily impacted by stress than other thyroid hormones. In a human study of physical and mental acute stress-induced endocrine changes, stress-altered levels of cortisol, TSH, and T4 returned to normal after 4 to 5 days of stress cessation; however, T3 suppression continued.[26] Because low T3 and mild hypothyroidism often go undiagnosed, learning to recognize the symptoms of mild hypothyroidism is important in supporting the optimal health of patients under stress (Figure 1).

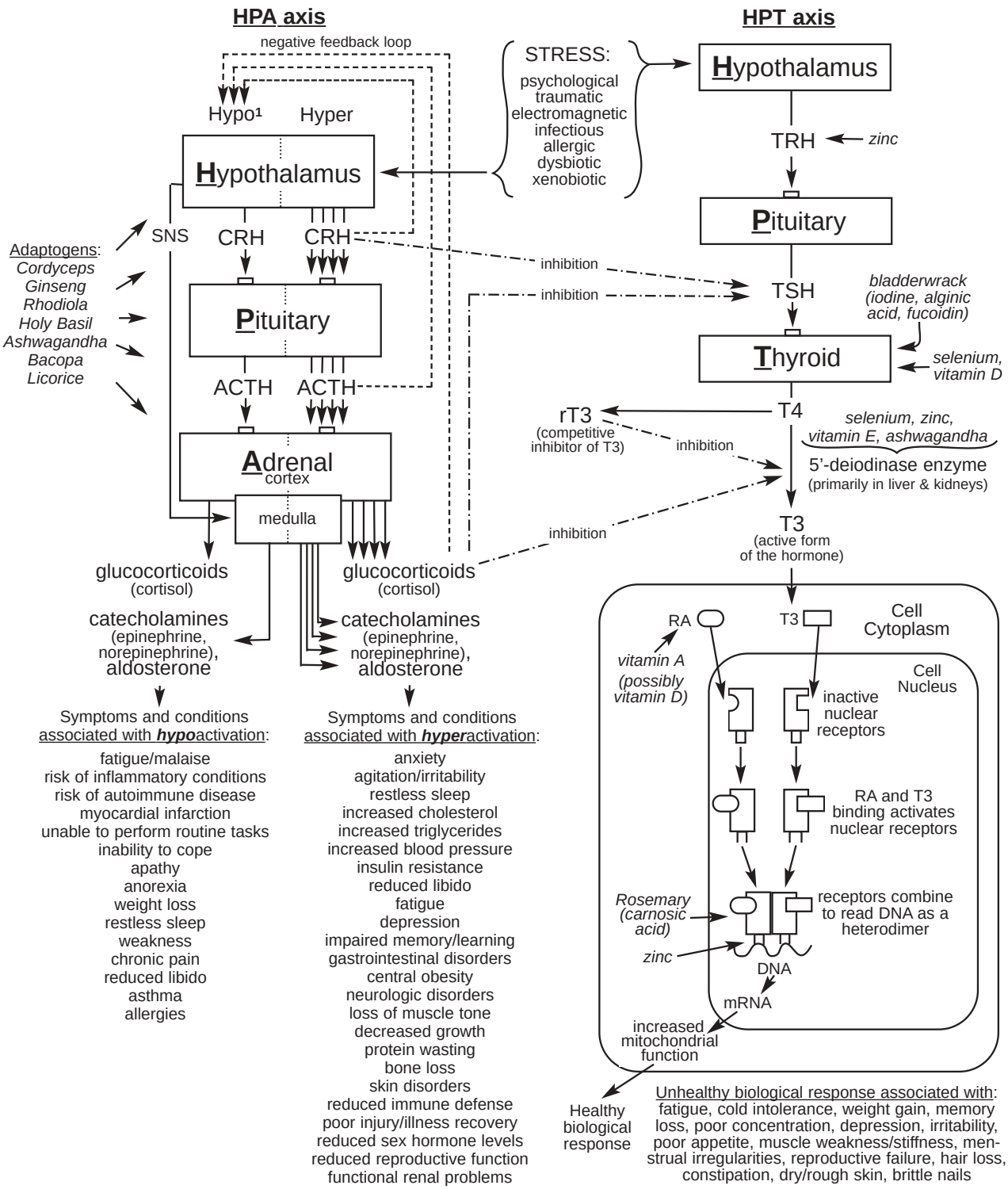
ADAPTOGENIC HERBS FOR SUPPORTING A HEALTHY STRESS RESPONSE

It is clear that the effects of stress and HPA dysfunction can be extensive. Fortunately, lifestyle changes such as stress reduction, relaxation, regular exercise, and a healthy diet can all support a healthy response to stress.[1] In addition, select herbs referred to as "adaptogens" that have been used over the centuries in traditional medicine have clear empirical and clinical evidence of their ability to support a healthy response to stress and normalize HPA activity.[27,28]

Through their complex chemical compositions, adaptogens are able to address multiple levels of the stress response, including HPA activation, feedback loops, GC excess or insufficiency, insulin and glucose homeostasis, energy levels, cognitive function, gastric mucosal strength, blood lipid levels, blood pressure, and immunity. These multiple applications and their ability to increase nonspecific resistance to stress are what define them as adaptogens.[27] Because of their complex chemical structure and their broad effects, herbal adaptogens provide the benefit of balancing and normalizing the physiology. This rationale is also a good argument for using whole herb extracts rather than isolated actives.

Holy Basil (*Ocimum sanctum*)—Holy basil is an Indian herb with a rich history, whose adaptogenic benefits are rapidly becoming evident to Western healthcare professionals. True to adaptogenic definition, holy basil has been found to affect mul-

Figure 1. The Effects of Stress and Nutritional Support on the HPA / HPT Axes



1. **Contributors to *hypo*activation of HPA**: a) reduced biosynthesis of CRH, ACTH, and cortisol due to organ hypofunction or depleted hormone precursors, b) CRH hypersecretion causing down-regulation of pituitary CRH receptors and reduced secretion of ACTH, c) increased negative feedback sensitivity, d) morphological changes (e.g., adrenal atrophy).

Acronym Key: ACTH: adrenocorticotropin hormone; CRH: corticotropin-releasing hormone; DNA: deoxyribonucleic acid; mRNA: messenger ribonucleic acid; RA: retinoic acid; rT3: reverse triiodothyronine; SNS: sympathetic nervous system; T3: triiodothyronine; T4: thyroxine; TRH: thyrotropin-releasing hormone; TSH: thyroid-stimulating hormone.

tiple aspects of physiology. Research suggests that it has immunomodulatory activities, enhances gastric mucosal strength, normalizes blood glucose levels, increases physical endurance, supports healthy blood lipid levels, and modulates adrenal corticosterone levels in animals.[27,29-34] Furthermore, CNS activities mediated by holy basil, such as enhanced motor activity, may relate to dopaminergic influences.[27]

In support of traditional and empirical data, holy basil has repeatedly been shown to modulate stress response activity in animal testing.[27,32,35] In rats, the incidence of gastric ulcer and psychobiological changes (aversiveness to restraint, struggle) induced by cold stress and restraint stress were markedly reduced by pretreatment with holy basil.[30,35] In addition, rats treated with holy basil have shown increased physical endurance and significantly lower cholesterol than untreated stressed groups.[29,30] In noise stress studies, treatment with holy basil prevented the increase in the plasma level of corticosterone induced by exposure to acute as well as chronic noise stress, and pretreatment with holy basil was able to normalize stress-altered values in white blood cells, corticosterone, and neutrophil function.[32,35]

Ashwagandha (*Withania somnifera*)—Known in the Indian system of Ayurveda as a classic rejuvenating herb, ashwagandha has repeatedly proven its adaptogenic potential. While the HPA-modifying mechanisms of ashwagandha are not fully understood, research suggests it may interact with pathways in the CNS that affect HPA activation and catecholamine production. These pathways may include cholinergic, GABAergic, and dopaminergic pathways.[27,36-38]

Animal testing suggests that ashwagandha enhances adaptability to both physical and chemical stress. Mice pretreated with ashwagandha and subjected to swimming stress showed increased endurance as compared to untreated mice, and did not show the adrenal hypertrophy, ascorbic acid depletion, or corticosterone depletion associated with the stress syndrome.[39,40] Ashwagandha also has anabolic activity and produces positive changes in stress-related prostaglandin and catecholamine production, blood glucose levels, and cholesterol levels. Its immunomodulating effects are also well-documented.[27,37,41] Additionally, ashwagandha has been shown to prevent ulcers and other symptoms associated with stress.[39] Also of interest, preliminary work in mice shows that ashwagandha increases T3 and T4 concentrations, perhaps by stimulating thyroidal activity and protecting hepatic tissue (involved in T4 to T3 conversion) from peroxidation.[42]

Bacopa (*Bacopa monnieri*)—In Ayurveda, bacopa is used to revitalize nerves, brain cells, and the mind, and to help strengthen the adrenals and purify the blood. In animal testing, bacopa has been shown to improve adaptations in sensory, motor, and motivational systems.[43,44] In humans, it exhibits beneficial effects on anxiety, as well as mental functions studied in terms of mental fatigue.[45] Its CNS effects are believed to be mediated via GABAergic systems.[46] In addition, other research indicates that a saponin derived from bacopa modulates noradrenaline and serotonin content of the brain.[47]

In a human study of the effects of bacopa on anxiety neurosis, one month of treatment (equivalent to 12 g/day crude herb) provided significant relief of symptoms—in addition to a quantitative reduction in the level of anxiety, maladjustment, and disability—all leading to improved mental function.[45] In addition, the level of urinary corticoids was reduced after treatment. In a double-blind, placebo-controlled human study, the effects of bacopa extract (300 mg/day) on cognition was studied.[48] The treated patients showed improved speed of visual information processing, learning rate, and memory as compared to placebo, with maximal effects evident after 12 weeks. The authors concluded that bacopa may improve cognitive processes that are critically dependent on input from our environment.

Cordyceps (*Cordyceps sinensis*)—Cordyceps is a therapeutic fungus found primarily at high altitudes in China. It is commonly known in China as "caterpillar fungus" and is one of the most valued medicinal fungi in Chinese medicine.[49,50] Research dating back to 1843 states that cordyceps has properties similar to those of ginseng, such that it is used to strengthen and rebuild the body after exhaustion or long-term illness.[50] In fact, traditional Chinese formulas designed to "tonify Qi," or promote proper organ function and energy production, consistently combine ginseng with fungi. Human clinical studies performed in China have documented the beneficial effects of cordyceps in the treatment of chronic obstructive hepatic disease, kidney toxicity, hypercholesterolemia, and other aging disorders, including loss of sexual desire.[49,50] In China, cordyceps is used specifically for excessive tiredness, persistent cough, impotence, debility, and anemia, as well as to support healthy function of the gonads.[50] Research has also demonstrated immunoregulating activities.[49,50]

To evaluate the effect of *C. sinensis* on energy metabolism, adult male mice were given 200 or 400 mg/kg/day or placebo for 7 days. The results indicated that the cordyceps was effective in improving bioenergy status in murine liver by increasing adenosine triphosphate (ATP). The authors speculate that this mechanism may underlie its observed clinical effectiveness in alleviating fatigue and improving physical endurance.[52] In another study, a polysaccharide purified from cultured mycelium of cordyceps significantly lowered the plasma glucose level in streptozotocin-induced diabetic mice and epinephrine-induced hyperglycemic mice after intraperitoneal injection (50 mg/kg).[53] For species identification of *C. sinensis*, and to guarantee consistent potency, standardization of actives such adenosine and cordycepic acid (d-mannitol) is recommended.[49-51]

Asian Ginseng (*Panax ginseng*)—Ginseng is greatly valued in traditional use as a tonic, a substance that acts to normalize the body, thereby helping to create a state of healthy homeostasis through a variety of pharmacological actions.[54] According to traditional Chinese medicine, the individual who will benefit from ginseng is overwhelmed and exhausted.[55,56] Thus, it is used to enhance stamina and the capacity to cope with fatigue and physical stress.

Although the exact mechanisms of ginseng remain a mystery, animal and human research suggests that ginseng may influence HPA activity by modulating GC levels; influencing the occupancy and sensitivity of positive and negative feedback stress hormone receptors; and inhibiting cortisone-induced adrenal and thymic atrophy.[27,54,57-59] Overall, ginseng seems to have a balancing effect on the HPA axis by modifying hormonal control of homeostasis therein.

In a multicenter, comparative, double-blind clinical study, the effectiveness of a supplement containing ginseng (80 mg/day) and various vitamins and minerals was assessed in patients with functional fatigue.[60] After 42 days of treatment with the ginseng supplement, statistically significant improvements were found in fatigue scores of the treatment group as compared with the placebo group.

P. ginseng contains multiple phytochemicals, however, many of the key actions of the herb have been associated with the indi-

vidual triterpenoid saponin glycosides, known as ginsenosides, isolated from the main root.[61] Analytical methods are now available using HPLC to quantify the ginsenosides in ginseng extracts. Using such analytical tools, researchers have found that a significant variation in the ginsenoside content of products exists.[61,62] The use of standardized, authentic ginseng main root preparations that supply a quantifiable amount of ginsenosides are recommended for consistency in the clinical setting. The effective dose of ginsenosides can vary from about 8 mg/day to as much as 116 mg/day, as calculated from European and Chinese literature.[61,63]

Rhodiola (*Rhodiola rosea*)—Rhodiola, also known as "Arctic root" or "golden root," is indigenous to and widely distributed at high altitudes in Arctic and mountainous regions throughout Eastern Europe and Asia. In the traditional medical practices of these countries, rhodiola is popularly used to stimulate the nervous system, decrease depression, enhance work performance, and eliminate fatigue.[64] Much of the early anti-stress research on rhodiola was performed by Russian researchers, who categorized it as an adaptogen due to its ability to increase resistance to a variety of chemical, biological, and physical stressors.[65,66]

Research suggests that the adaptogenic, cardiopulmonary, and CNS activities of rhodiola are largely attributed to its effects on the levels and activity of monoamines (serotonin, dopamine, catecholamine) and opioid peptides, such as beta-endorphins.[65,67] In addition, rhodiola has been reported to prevent the depletion of adrenal catecholamines induced by acute stress; help maintain normal levels of cyclic adenosine monophosphate (cAMP) in myocardium, which produces a cardioprotective effect; and support immune function by stimulating specific immune defenses.[64,66,68] Unlike other rhodiola species, *R. rosea* has been used for more than 35 years in animal and human testing.[64]

Double-blind, placebo-controlled clinical trials provide strong evidence that rhodiola possesses high biological activity with no detectable toxicity.[64] One study of work-fatigued physicians showed a 20% positive change in speed of visual and audio perception, attention capacity, and short-term memory after 2 weeks of supplementation with 170 mg/day *R. rosea* (containing approximately 4.5 mg salidroside).[66] Another study measured the stimulating and normalizing effect of rhodiola extract (1,100 mg/day) on students during a stressful examination period. The most significant improvements were seen in physical fitness, mental fatigue, and neuro-motor tests.[69]

Licorice (*Glycyrrhiza glabra*)—Of the many herbs available, licorice root is one of the most highly regarded in terms of treating conditions associated with diminished adrenal function. Licorice is known to have multiple pharmacological actions including adrenocorticoid-like activity.[55,70] In addition, licorice has antiinflammatory, antitussive, antiviral, antiulcer, and estrogen-balancing properties.[71-73] The adrenocorticoid activity of licorice is associated with two active components—glycyrrhizin and glycyrrhitinic acid. These actives have been reported to bind to both glucocorticoid and mineralcorticoid receptors, possibly displacing endogenous steroids and thus contributing to an increase in availability of cortisol within the body.[74] Additionally, research suggests that glycyrrhizin and/or glycyrrhetinic acid increase the half-life of circulating cortisol in the body by inhibiting its enzymatic breakdown via 11β-hydroxysteroid dehydrogenase.[75] In one study, glycyrrhetinic acid was shown to delay the clearance of cortisol in patients with adrenocortical insufficiency and in patients who had been taking oral prednisolone medication for at least 3 months.[76]

It is important to note that due to the mineralcorticoid effect of glycyrrhizin or glycyrrhetinic acid, excessive or prolonged licorice intake can cause sodium and water retention with resultant hypertension and hypokalemia. Patients therefore need to be regularly evaluated for signs of pseudoaldosteronism when taking licorice preparations.[75] A dose of 200-800 mg/day for 4-6 weeks is generally recommended. For long-term use (reevaluation at 6 months), the dosage should be reduced to approximately 100 mg/day.

NUTRIENTS THAT SUPPORT THYROID HORMONE FUNCTION

Normalizing stress-induced changes in HPA function will have a positive influence on the normal function of the HPT axis; however, for some patients, optimal thyroid hormone function should be addressed at multiple levels. Several nutrients are known to support healthy thyroid hormone synthesis, to promote the conversion of T4 to the more bioactive T3, to address receptor dynamics and enhance nuclear binding and the expression of thyroid hormone responsive genes, and to help reduce the risk of autoimmune thyroid dysfunction. Supplementation with these nutrients can provide the added support many patients may need.

Bladderwrack: A Natural Source of Iodine—Bladderwrack (*Fucus vesiculosus*) is an algae found on submerged rocks along the coasts of North America and Europe.[77] It is a source of iodine, which supports thyroid hormone synthesis.[78] Bladderwrack may benefit thyroid function not only by providing iodine, but also because the iodine-containing compounds in bladderwrack may compete for uptake of potentially toxic compounds. There is also evidence that polysaccharides in bladderwrack may bind heavy metals, such as lead, mercury, and cadmium, which can interfere with thyroid function.[79] Bladderwrack has been traditionally used to treat hypothyroidism, as well as obesity and atherosclerosis.[78,79]

Normal thyroid function is dependent on many trace elements for the synthesis and metabolism of thyroid hormones, and iodine is the most important of these. In the thyroid gland, iodine is sequestered, oxidized, and bound to tyrosine to produce thyroglobulin. Thyroglobulin is then transformed into diiodothyronine, which is then converted to T4. The clinical outcomes of iodine deficiency range from mild hypothyroidism to severe endemic cretinism.[20] New data indicate a sharp decline in iodine intake in the U.S. during the last 20 years, especially in women of reproductive years.[80]

Selenium—Due to its role as a cofactor for the iodothyronine deiodinase enzymes and selenoproteins (glutathione peroxidase enzymes) that regulate thyroid hormone synthesis and preserve thyroid integrity, selenium is essential for normal thyroid hormone production and metabolism.[19,20,81] Sufficient selenium is important for healthy conversion of T4 to T3, and perhaps to avoid elevated rT3. The conversion of T4 to T3 is catalyzed by the selenium-dependent enzyme 5'-deiodinase, while the conversion of T4 to rT3 is catalyzed by a non-selenium dependent enzyme.[19,81] Therefore, when selenium is deficient, T4 may be preferentially converted to rT3.

Selenium is deficient in nearly 50% of diets, which may account for a significant percentage of those with low thyroid hormone activity.[21] In a double-blind, placebo-controlled trial of selenium supplementation (100 mcg/day for 3 months) among elderly subjects, an improvement in selenium indices, a decrease in T4, and a trend toward normalization of the T3:T4 ratio was observed.[82] In selenium-deficient uremic patients, 6 months of

selenium supplementation at 500 mcg 3 times weekly for the first 3 months and 200 mcg 3 times weekly for the following 3 months reduced rT3, increased free T3, and reduced TSH levels.[83]

Zinc—Zinc may play many roles in thyroid hormone homeostasis. It is involved in the synthesis of TRH; a zinc deficiency may lower 5'-deiodinase function, thereby contributing to a lower conversion of T4 to T3; and preliminary research suggests that zinc may play a role in the healthy expression of thyroid hormone responsive genes by influencing transcription factors that affect T3 nuclear receptor interactions.[19,20,84] To examine zinc status in relation to thyroid function, 13 patients that had low T3 and normal T4 were selected. Nine of the 13 had mild to moderate zinc deficiency. After oral supplementation of zinc sulfate (4-10 mg/kg body weight) for 12 months, levels of T3 normalized, serum rT3 decreased, and TRH-induced TSH reactions improved.[84] In another study, healthy adult men fed a low zinc diet (5.5 mg/day) tended to show decreases in serum TSH and T4 and an increase in TSH and T4 when an adequate zinc diet was fed.[85]

Vitamin E—Animal research suggests that vitamin E may support the conversion of T4 to T3 by influencing hepatic 5'-deiodinase activity. It may accomplish this by protecting the stability of cell membranes in which 5'-deiodinase exists.[86]

To study the effect of vitamin E against lead-induced deterioration of cell membranes associated with 5'-deiodinase, mice were simultaneously administered vitamin E (5 mg/kg body weight) and lead. The results showed that T3 and hepatic 5'-deiodinase activity were maintained within normal levels.[87] In another animal study, cadmium administration decreased hepatic 5'-deiodinase by 90% and reduced T3 concentration by 69%, without altering T4. Administration of vitamin E (5 mg/kg body weight on alternate days) restored thyroid function by maintaining normal 5'-deiodinase activity and reducing lipid peroxidation.[88]

Vitamins A and D: The Prohormones—Like T3, vitamin A (retinoic acid) and vitamin D (1,25-dihydroxycholecalciferol) are hormones that affect gene expression by binding nuclear receptors.[89] Research suggests that vitamin A may provide functional support that contributes to the regulation of thyroid hormone-responsive genes.[22,89,90] As an example, T3 and retinoic acid bind to and activate their individual receptors within the nucleus. These hormone/nuclear receptor complexes can combine to form what is known as a heterodimer that binds to and supports the transcription of DNA.[90] The binding of T3 receptors to DNA may be enhanced by heterodimerization, thereby supporting the expression of thyroid hormone responsive genes (Figure 1).[91] In related preliminary in vitro research, carnosic acid from rosemary (*Rosmarinus officinalis*) has been shown to increase the expression of vitamin D and retinoid receptors.[92] It may be postulated therefore that carnosic acid may increase the opportunity for heterodimerization, thereby supporting T3-mediated gene transcription.

In a study to identify the effect of vitamin A deficiency on T3, young rats were given a diet with or without vitamin A for 7 weeks. In rats on a vitamin-A deficient diet the formation of T3 complexes with nuclear proteins was reduced, and a decreased binding capacity of nuclear T3 receptors to DNA was observed. These rats had decreased growth and decreased activity in lipogenic enzymes, both thought to be related to the decreased formation of T3 nuclear complexes.[93] In a study of hypothyroid rats, the T3 binding capacity was unaltered by administration of T3 or retinoic acid alone, but increased by 48% after treatment with T3 and retinoic acid together.[94]

Some researchers believe that new information on vitamin D as a gene expression modulator interacting with T3 and retinoic acid is forthcoming. Currently, research suggests that vitamin D deficiency, a common finding in aging populations, is associated with an increased incidence and severity of autoimmune disease.[95] Furthermore, vitamin D administration has been shown to suppress the development of autoimmunity in experimental animal models. Mechanisms seem to involve vitamin D's inhibitory effect on interleukin-2 and interferon gamma—increased levels of these compounds have been associated with thyroiditis and primary hypothyroidism.[95-97]

Chronic stress-induced dysfunction of the HPA and HPT axes can create significant loss of vitality, as well as serious long-term health problems. While stress is an inevitable consequence of modern life, the downstream damage caused by chronic stress is not. Having a positive attitude, keeping things in perspective, and taking care of the mind and body are all critical to avoid being consumed by daily stressors. A healthy diet, regular exercise, and relaxation, in addition to adaptogenic herbs that help normalize parameters of the stress response and nutrients that support optimal thyroid hormone activity, can support overall health and well-being throughout life.

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NUTRITIONAL MANAGEMENT OF STRESS-INDUCED DYSFUNCTION: A SUMMARY

By Richard L. Shames, M.D.

In today's fast-paced society, the vast majority of individuals are under a constant barrage of stressors. Surveys and research reports conducted over the past two decades reveal that 43% of all adults suffer adverse effects due to stress. In fact, 75% to 90% of all visits to primary care physicians are in some way related to the adverse impacts that stress has on the body.[1]

THE HYPOTHALAMIC-PITUITARY-ADRENAL (HPA) AXIS

Stressors trigger the HPA axis. The HPA axis then translates these stressors into signals that alter the body's biochemistry to support a "fight or flight" response, also termed the stress response. The HPA axis is the primary regulator of this stress response. While stress-induced changes in biochemistry may be beneficial to survival in the short term (acute stress), they present an increased risk of various health challenges in the long term (chronic stress).[2-4]

Dysfunction of the HPA axis brought on by repeated exposure to stressors may curtail life expectancy by several years due to its downstream effects on physiology and organ/system function.[4,7] Research increasingly supports the critical role that stress can play in obesity, diabetes, osteoporosis, hypertension, cardiovascular disease, infectious disease, gastric ulcer, cancer, and gastrointestinal, skin, psychological, and neurologic disorders, as well as a host of disorders linked to immune system disturbances.[1,4,5,7-11]

COMBATING STRESS WITH HERBAL ADAPTOGENS

Fortunately, lifestyle changes such as stress reduction, relaxation, regular exercise, and a healthy diet can all support a healthy response to stress. In addition, many herbs referred to as "adaptogens" have been used over the centuries in traditional medicine and have clear empirical and clinical evidence of their ability to support a healthy response to stress and normalize HPA activity.[27] Adaptogens, by nature, have a variety of beneficial effects, such as increasing energy and stamina, preventing fatigue, enhancing memory and concentration, and improving work performance.[27,28] Such adaptogenic herbs include:

Holy Basil (*Ocimum sanctum*)—Holy basil is an Indian herb with a rich history of treating a variety of conditions. It has repeatedly shown to modulate stress response activity in animal testing. For instance, treatment with holy basil decreased the incidence of gastric ulcer, increased physical endurance, and lowered the stress-induced release of adrenal hormones and cholesterol in animal studies.[27,29-35]

Ashwagandha (*Withania somnifera*)—Known as a classic rejuvenating herb in Indian medicine, ashwagandha has been shown to enhance adaptability to both physical and chemical stress. For instance, mice pretreated with ashwagandha and subjected to physical stress showed increased endurance. Additionally, ashwagandha has been shown to prevent ulcers and other symptoms associated with the stress response.[27,36-38]

Bacopa (*Bacopa monnieri*)—Bacopa is traditionally used to revitalize nerves and the mind, as well as to help strengthen the adrenals. In animal testing, bacopa has been shown to improve adaptations in sensory, motor, and motivational systems.[43-48]

Cordyceps (*Cordyceps sinensis*)—Cordyceps is a therapeutic fungus found primarily at high altitudes in China and is one of the most valued medicinal fungi in Chinese medicine. Research dating back to 1843 suggests the use of cordyceps to help strengthen and rebuild the body after exhaustion or long-term illness.[49-53]

Asian Ginseng (*Panax ginseng*)—Ginseng is greatly valued as a tonic—a substance that acts to normalize body function and biochemistry. According to traditional Chinese medicine, the individual who will benefit from ginseng is overwhelmed and exhausted.[54-59]

Rhodiola (*Rhodiola rosea*)—Rhodiola is widely distributed at high altitudes in the Arctic and mountainous regions throughout Eastern Europe and Asia, where it is traditionally used to stimulate the nervous system, decrease depression, enhance work performance, and eliminate fatigue.[64-66]

Licorice (*Glycyrrhiza glabra*)—Of the many herbs available, licorice is one of the most highly regarded in terms of treating conditions associated with diminished adrenal function.[55-70]

THE HPA/THYROID LINK

Stress-induced HPA dysfunction may also hinder the proper function of the metabolic regulator, the thyroid. Research suggests that high levels of stress affect the synthesis of thyroid hormones (T4, T3) and negatively impacts their metabolism.[19,20] The end result is reduced thyroid hormone activity and the accompanying health challenges, which include weight gain, lethargy, reproductive failure, depression, irritability, memory loss, muscle weakness, and more serious long-term effects, such as congestive heart failure.[23]

NUTRITIONAL SUPPORT FOR HEALTHY THYROID HORMONE ACTIVITY

Specific combinations of nutrients may support 1.) thyroid hormone synthesis, 2.) the conversion of T4 to the more bioactive T3, and 3.) the expression of thyroid hormone responsive genes. Taken together these activities may promote the optimal health of individuals with thyroid hormone issues originating from insufficient metabolism or activity of thyroid hormone. These nutrients include:

Bladderwrack—Bladderwrack is an algae that provides a natural source of iodine, which is required for the synthesis of T4 in the thyroid gland.[77,78]

Selenium—Due to its role as a cofactor for the enzyme 5'-deiodinase, which converts T4 to T3, selenium is essential for normal thyroid hormone metabolism and biological activity.[19,20,81]

Zinc—Research suggests that zinc may play many roles in thyroid hormone homeostasis, including supporting T4 synthesis, 5'-deiodinase function, and healthy expression of thyroid hormone responsive genes.[19,20,84]

Vitamin E—Vitamin E may support the conversion of T4 to T3 by influencing hepatic 5'-deiodinase activity; it may accomplish this by protecting the stability of cell membranes in which 5'-deiodinase exists.[86-88]

Vitamins A, D, and Carnosic Acid—These nutrients may provide support for the binding of thyroid hormone receptors to DNA, thereby contributing to the healthy expression of thyroid hormone responsive genes.[22,89-94]

While stress is an inevitable consequence of modern life, the downstream damage caused by chronic stress is not. A healthy diet, regular exercise, and relaxation are important factors in managing stress. In addition, adaptogenic herbs that help normalize parameters of the stress response and nutrients that support optimal thyroid hormone activity play an important role in supporting overall health and well-being throughout life.