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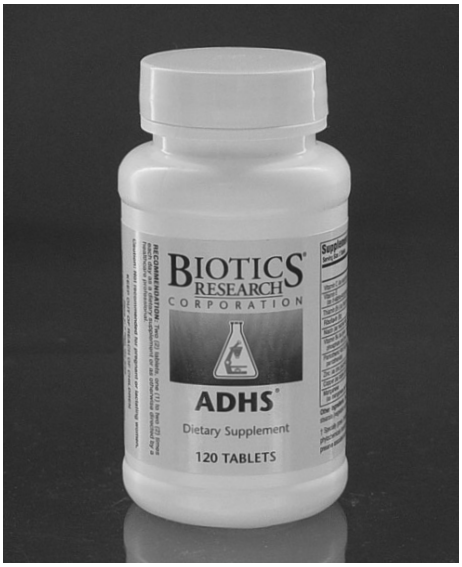

Adrenal Hormones and Adaptation to Stress

Stress, is one word that has become synonymous with the American lifestyle. America has become a "stressed out" society. The phenomenon that has become such a part of our daily vocabulary was coined over seventy years ago by Hans Selye.[1] He described the occurrence as nonspecific bodily changes that transpired in response to physically harmful stimuli.[2] In his reporting Selye also indicated that although the adrenal glands are the first glands to respond to stress, they are also the first glands to fail under stressful conditions. The body possesses a complex system for adapting to stressful conditions. The ability of the organism to adjust homeostasis and in turn increase the chance of survival is dependent upon the activation of the stress system. This activation in turn leads to both behavioral and peripheral changes.[3]

The adrenal glands, a pair of triangular structures located atop each kidney, play a key role in stress adaptation and regulation. Not only are they necessary for life, but they also play an essential role in energy production and in controlling the conversion of carbohydrate, protein and fat into blood glucose. Moreover they partake in the fluid and electrolyte balance of cells, in the interstitial fluids, the blood stream, as well as in fat storage. They are also an important component in the production of sex hormones, especially following menopause.

The adrenal cortex secretes four major groups of hormones, classified as the glucocorticoids, the mineralcorticoids, androgens and estrogens. The adrenal medulla is responsible for the secretion of the catecholamines, particularly epinephrine and norepinephrine. The secretion of all adrenal steroids, including the glucocorticord cortisol, is under the control of pituitary adrenocorticotropic hormone (ACTH), which functions by a negative feedback mechanism. Consequently, a high level of circulating cortisol will suppress the secretion of ACTH, while a drop in cortisol will result in an increased ACTH secretion.[4] The action of the glucocorticoids is catabolic, stimulating the breakdown of protein and the inhibition of protein synthesis. Increased cortisol in the circulation initiates fat deposition in adipose tissue, and consequently weight gain is common with cortisol excess. Blood glucose homeostasis is also affected by cortisol, and its action is two-fold, via the stimulation of hepatic gluconeogenesis and via the inhibition of glucose uptake by tissues. Additionally, both the inflammatory and immune responses are suppressed by glucocorticoids, and thymic and lymph atrophy are known to develop in the presence of excess cortisol.[4]

Cortisol, the prototype of the glucocorticoids, is the hormone synthesized in the greatest quantity by the adrenal glands; approximately two hundred fold that of aldosterone. It exerts numerous physiologic actions on the body, including maintenance of normal blood pressure, regulation of fluid and electrolyte balance, protein metabolism, body fat distribution, glucose metabolism, and normal muscle formation. It also exerts action on both the hematopoietic system (blood cell formation) and on the lymphatic tissues.[4] Secretion is perform in a diurnal pattern, with the highest value between 6 and 8 a.m., and the lowest normally around midnight.

Dysregulation of the stress system or a maladaptive neuroendocrine response has the potential to result in disturbances in growth and development, and may ultimately result in other health consequences including psychiatric, endocrine/metabolic, and/or autoimmune imbalances, as well as vulnerability to such diseases.[5] It has been documented that stress-induced hypercortisolism and visceral obesity and their cardiovascular and other sequelae increase the all-cause mortality risk of affected subjects by 2-3-fold, and curtail their life expectancy by several years.[3] If not controlled ACTH hypersecretion frequently results in Cushing's disease.[6] Other diseases have been correlated to an excess production of adrenal androgen. For example it has been estimated that in patients with polycystic ovarian syndrome, 20-30% produce an excess of adrenal androgen, resulting in elevated levels of dehydroepiandrosterone sulfate (DHEAS). Accordingly in patients with PCOS, as a consequence of the response to ACTH stimulation a "generalized hypersecretion of adrenocortical products" has been observed.[7]

Nutritional Support for Adrenal Function

An extensive body of research provides important insights into nutritional support for adrenal function. Additionally, stress increases the need for many nutrients. A variety of factors affects the function of the adrenal glands, and may include dietary, environmental and/or innate mechanisms. Dietary factors are important contributors of adrenal stress. For example excess dietary carbohydrates or diets low in protein put additional stress on the adrenals. Inadequate or poor quality water also affects the adrenals due to inadequate oxygenation of the tissues. Prolonged or persistent hyperfunction may consequently result in disease outcomes, including Cushing syndrome, hyperaldosteronism, or adrenogenital syndromes.[8] An additional end result of adrenal hyperfunction is the excess production of one of the three corticosteroids; cortisol, aldosterone or adrenal androgens.

In children and adolescents adrenal hyperfunction may ultimately result in stunted growth and short stature in adults. Growth hormone was also observed to be low in patients with adrenal hyperfunction.[9, 10] Consequently, adrenal stress results in a greater need for many nutrients.

Amino Acids for Catecholamine Synthesis

L-Tyrosine is a conditionally essential amino acid. This key raw material is a precursor for the synthesis of catecholamines, epinephrine, norepinephrine, dopamine, thyroxine (T_4) and triiodothyronine (T_3). Stress increases the release of catecholamines, which in turn may result in depletion of their levels. As a precursor of the catecholamies, alterations in L-tyrosine availability result in an influential response in the synthesis of dopamine and norepoinephrine. This effect can be minimized by the use of supplemental L-tyrosine.[11]

Vitamins associated with Adrenal Support

Vitamin C (as ascorbic acid). The concentration of vitamin C in the adrenal glands is among the highest in the body, being roughly 100 times that of blood plasma levels.[12] As such they are extremely sensitive to deficiencies in vitamin C. In catecholamine synthesis, vitamin C is required as a co-factor in the conversion of dopamine to

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norepinephrine.[13] In humans vitamin C secretion occurs as part of the stress response via hormone regulation, specifically in response to stimulation via the hormone adrenocorticotrophic (ACTH). Following ACTH stimulation the mean adrenal vein vitamin C level increases approximately four fold, and then subsequently returns to near pre-stimulation levels approximately 15 minutes thereafter. Peak adrenal vitamin C and cortisol concentrations have been strongly correlated (r^2=0.35, P<0.001), suggesting a local action of vitamin C on the adrenal glands. Additionally, it has been noted that, although being of unknown function, the increase in vitamin C secretion suggests that "adrenal vitamin C secretion is an integral part of the stress response."[14] Stress, fever and viral infections, as well as habitual actions, such as smoking and alcohol use, cause a rapid decline in the blood level of vitamin C.[15]

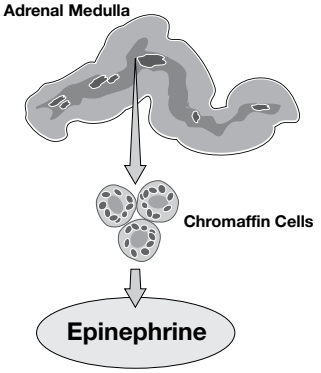
Pantothenic Acid (as calcium pantothenate). Pantothenic acid is a cofactor in the synthesis of coenzyme A (CoA). CoA plays an important part in cellular respiration, as well as in the biosynthesis of many important compounds including fatty acids, cholesterol and acetylcholine.[16] Animal studies have documented morphological damages in the adrenal cortex with pantothenic acid deficiency.[17,18,19,20,21,22] Early experiments in animals also indicated that following prolonged pantothenic acid deficiency, extensive damage to the adrenal resulted, which was attributed to the adrenals inability to immediately utilize pantothenic acid. It was thus concluded that pantothenic acid deficiency results in an imposed stress upon the adrenal cortex, which in turn results in exhaustion and consequently adrenal hypofunction.[23] In spite of the fact that deficiencies are generally thought of as being rare, a deficiency in pantothenate results in fatigue and generalized malaise.[24]

Vitamin B_6 (as pyridoxal-5-phosphate and pyridoxine HCl). Vitamin B_6 serves as a coenzyme in well over 100 reactions, most of which are transaminase reactions. It plays an important role in the synthesis of the neurotransmitters γ-aminobutyric acid (GABA), serotonin, dopamine, norepinephrine and epinephrine.[25] As a physiological modulator of steroid hormone action, Vitamin B_6 has been associated with modulation of the expression of a diverse array of hormonally responsive genes.[26] For efficient function both the nervous and immune systems require an adequate supply of vitamin B_6.[27,28,29,30] Vitamin B_6 is also required for the conversion of tryptophan to niacin and serotonin,[31,32] as well as for the conversion of tyrosine to dopamine. In one study a deficiency in vitamin B_6 was correlated to a slower extracellular dopamine release (43% longer with deficiency).[33] Dopamine is known to be an active participant in the secretory modulation of both aldosterone and catecholamine from the adrenal gland.[34] Dopamine depletion is correlated with physical and/or psychological stress.

Vitamin E (as d-alpha tocopheryl acetate). Vitamin E is found in all cells in the human body, and functions primarily as an antioxidant. The adrenal cells, along with the pituitary, platelet and testicular cells contain the highest cellular concentration of vitamin E.[25] In animal studies vitamin E deficiency was demonstrated to predispose tissues to lipid peroxidation.[35] Conversely, vitamin E therapy affords protection against the effects of mineral toxicity, attributed to reversing the alterations in adrenocortical activities brought on by toxic mineral levels. In another study treatment with alpha tocopherol during times of significant stress was demonstrated to decrease lipid peroxidation in both the liver and the brain, while simultaneously preventing depletion in glutathione levels, which are routinely depleted by stress.[37] Adrenal sensitivity to ACTH is also increased with vitamin E therapy.[38]

Thiamin (as thiamin mononitrate). Thiamin, a water-soluble B-complex vitamin, is involved in many bodily functions, including its requirement in the metabolism of carbohydrates, as part of the coenzyme thiamin pyrophosphate (TPP). In the absence of thiamin, a slowing or complete blocking of enzymatic activity occurs. As part of the citric acid cycle, essential for energy production, thiamin functions as a component in the decarboxylation of α-ketoglutaric acid to succinyl CoA.[25] In animal studies corticosterone levels, have shown to be significantly increased with thiamin deficiency.[39,40]

Riboflavin. Like thiamine, riboflavin is also a water-soluble vitamin. It participates in normal cell function, growth and energy production. Riboflavin serves as a crucial component in converting food into energy via the manufacturing of flavin adenine dinucleotide (FAD). FAD is required for electron transport and ATP production in the Krebs cycle. Ariboflavinosis (riboflavin deficiency) is associated with weakness, cheilosis (fissures in the skin at the angles of the mouth), angular stomatitis (inflammation of the mucous lining of the mouth) and anemia. Individuals particularly susceptible to deficiency include the elderly, those with chronic illnesses or those with alcohol dependency.[41] Stress increases the need for riboflavin due to an increase in fatty acid oxidation. Riboflavin deficiency has been correlated to adrenal cortex dysfunction in animals.[42]



Niacin. Niacin's primary cellular function is as a coenzyme for NAD^+ and $NADP^+$, both of which function in the maintenance of cellular oxidation-reduction reactions. In addition to its varied cellular functions, NAD is used as a substrate for the production of poly-ADP-ribose (PARP). PARO is a nuclear enzyme activated by DNA strand breaks, which functions to synthesize polymers of ADP-ribose molecules, making it an important component in DNA repair.[43] Niacin intake has also been correlated with anxiety reduction.

Minerals associated with Adrenal Support

Minerals can also be a beneficial component for adrenal support, as an aide to sustaining the adaptogenic response of the adrenals.

Zinc. Zinc participates as an active component in over 300 different enzymes, and plays a vital role in many biological processes. As a cofactor for the antioxidant enzyme superoxide dismutase (SOD) it is an important component in cellular protection. It also functions in enzymatic reactions in both carbohydrate and protein metabolism.[41] Zinc deficiency and adrenal stress have been associated. One study noted a correlation between zinc deficiency and prostaglandin production, designating that with deficiency interference in the production and/or function of the prostaglandins ensues.[44]

Copper. Like zinc and iron, copper is also involved in gene regulation and expression, specifically for the metallothioneins, or metal-binding proteins. Studies have suggested that copper plays a role in mitochondrial gene expression, noting a decrease in oxidative phosphorylation with deficiency. A number of enzymes require copper as a cofactor and copper is necessary to balance zinc.

Manganese. Manganese (Mn) is a required mineral for optimal adrenal glandular activity. It serves as a component for energy metabolism, as a cofactor for enzymes of the citric acid cycle, as well as a functional cofactor as a as part of the enzymatic structure of several additional enzymes. As an essential cofactor for Mn superoxide dismutase (MnSOD), it is an important participant in the cellular antioxidant defense mechanism.[45] It also functions as an important modulator in signal transduction pathways.[46] Recent evidence has denoted a correlation between Mn deficiency and the balance of endothelium-derived prostanoids, indicating the presence of oxidative stress in Mn deficiency, as a result of reduced activity MnSOD, a major antioxidant enzyme.[47]

Lithium and Rubidium. Trace amounts of these two minerals are included as both are regarded as relaxant minerals. Additionally, lithium has been shown to have general neuroprotective effects,[48] as well as to offer protection against glutamate excitotoxicity, and to offer CNS neuroplasticity,

which was demonstrated in animals via molecular mechanisms.[49] The trace mineral rubidium (Rb) resembles potassium in terms of its method of absorption and excretion. In one study treatment with lithium or rubidium resulted in a decreased dopamine output.[50]

Botanical Extracts for Adrenal Support

A number of botanicals have properties identified as an aide in normalizing either excessive or deficient pathologies, with corresponding negligible disturbance in physiological function. In addition to established nutrients, several herbal extracts help support normal adrenal function. Many of these have their origins in Chinese or Ayurvedic traditions.

Achyranthes (extract)(root). In the Chinese pharmacology the action of Achyranthes is said to invigorate the blood, and to expel blood stasis. It is used in Yang tonic formulations. Its functionality is said to revolve around its ability to guide other herbs to the kidneys, genitals, and legs.

Damiana (extract)(herb) (*Turnera diffusa*). Damiana is a small shrub with an aromatic leaf, found predominantly in Mexico, Southern and Central America. Like Achyranthes, Damiana is also designated as a yang tonic, and is suggested to aide with energy. It is considered a strengthener for the nervous system, and is viewed as a nervous restorative.[53,54] Its properties are indicated as nerve stimulating, diuretic, aphrodisiac, and as being superior for impotence in men and frigidity in women.[55, 56] Traditional use is as a general tonic for the nervous, endocrine, and reproductive systems.[41]

Gotu Kola (extract)(herb) (*Centella asiatica*) – In Ayurvedic medicine Gotu Kola is an herb viewed as an important component in rejuvenation, as well as one of the chief herbs for revitalizing the nerves and brain cells. The following properties have been attributed to its actions; mildly antibacterial, anti-viral, anti-inflammatory, anti-ulcerogenic, anxiolytic, a cerebral tonic, a circulatory stimulant, a diuretic, nervine and vulnerary.[56] Punturee, *et al* demonstrated that *C. asiatica* has immunostimulating activity regarding both non-specific cellular immune responses and humoral immune responses. Additionally, they noted the inhibition of TNFα with an ethanol extract of *C. asiatica*, implicating that it may be an important component in downregulating inflammation.[57]

Sichuan Teasel (extract)(root) (*Dipsacus asperoides*) According to the Chinese tradition, *Dipsacus asperoides* (DA) is said to tonify the liver and kidneys, and to promote the movement of blood.[58] A crude polysaccharide fraction (DAP-1) from the root of DA has been shown to have a stimulating effect on the mitogenic activity of lymphocytes, as well as to suppress the phagocytic activity of macrophages.[59] DA has also demonstrated antinociceptive effects in a dose-dependent manner (from 3.75 to 30 mcg).[60]

Asiatic Dogwood. (extract)(fruit) (*Cornus officinalis*). *Cornus officinalis* (CO) is popular in traditional medicine and is known for its tonic, analgesic, and diuretic properties.[61] In addition to its use as a tonifier for liver and kidney deficiency, indicated by such symptoms as lightheadedness and dizziness, it is also said to tonify the essence and assist the yang.[58] The aglycons of anthocyanins have been shown to possess strong antioxidant activities.[62,63] Likewise, the anthocyanins of CO were also demonstrated to possess strong antioxidant activity.[64]

Basil (extract)(leaf) (*Ocimum basilicum*). Basil is a popular culinary herb, as well as a medicinal herb in Thailand, India and Turkey.[65] It is said to affect the lungs and stomach meridians, and its actions are indicated as being stimulatory to the adrenal cortex.[66] The chief compounds isolated from basil include eugenol, citral and geraniol,[67] as well as rosmarinic acid, a natural phenolic compound shown to inhibit complement-dependent inflammatory processes.[68]

Schisandra (extract)(fruit) (*Schisandra chinensis*). *Schisandra chinensis* (SC) has been utilized in traditional Chinese medicine (TCM) for over 2,000 years, as both a tonic and a sedative. As a tonic, one of its uses was to improve mental functions. It is considered an adaptogenic herb, which functions in the harmonization of the system. More recently, SC has been utilized to 'increase resistance to disease and stress, boost energy levels (without the jitteriness attributed to caffeine), increase both mental and physical endurance, and to improve vision, muscular and immune system.[69] Modern Chinese research suggests that SC may have a protective effect on the liver as well as possessing immunomodulting properties.[70] Gomisin A (GA), an isolated component from SC was demonstrated to cause a concentration-dependent vascular relaxation of the rat thoracic aorta.[71]

***Tinospora cordifolia* (extract)(stem & root)** The use of *Tinospora cordifolia* (TC) for debility, fever and dyspepsia in Ayurvedia is commonly recognized. The root of TC is documented as having anti-stress properties, as well as immune supporting properties.[72,73] An aqueous extract of TC has shown to be beneficial with adrenaline-induced hyperglycemia.[74,75,76]

ADHS® provides nutritional support for the adrenals in a non-glandular formula, consisting of herbal adaptogens, and supportive vitamins and minerals. It aids in supporting bodily functions when the body is under stress, and in supporting normal cortisol values, which may be especially important in obesity, Syndrome X and hyperinsulinism. Stress, a poor diet and environmental toxins are also contributors of adrenal malfunction, as referred to by Hans Selye's as "diseases of civilization." [77]

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Supplement Facts

Serving Size: 2 Tablets **Servings Per Container: 60**

	Amount Per Serving	% Daily Value
Vitamin C (as ascorbic acid)	100 mg	187%
Vitamin E (as d-alpha-tocopheryl acetate)	30 IU	100%
Thiamin (B_1) (as thiamin mononitrate)	2 mg	133%
Riboflavin (B_2)	2 mg	118%
Niacin (as niacinamide)	12 mg	60%
Vitamin B_6 (as pyridoxal-5-phosphate)	4 mg	200%
Pantothenic Acid (as calcium pantothenate)	30 mg	300%
Zinc (as zinc gluconate)	5 mg	33%
Copper (as copper gluconate)	0.5 mg	25%
Manganese (as manganese gluconate)	1.5 mg	75%

	Amount Per Serving	% Daily Value
Proprietary Blend	513 mg	
Lithium (from vegetable culture†)		*
L-Tyrosine		*
Achyranthes (extract) (root)		*
Damiana (extract) (leaf)		*
Gotu Kola (extract) (herb)		*
Sichuan Teasel (extract) (root)		*
Asiatic Dogwood (extract) (fruit)		*
Basil (extract) (leaf)		*
Shisandra chinensis (extract) (fruit)		*
Tinospora cordifolia (extract) (stem & root)		*
Rubidium (from vegetable culture†)		*

***Daily Value not established**

Other ingredients: Stearic acid (vegetable source), silica, modified cellulose gum, food glaze, and magnesium stearate (vegetable source).

† Specially grown, biologically active vegetable culture containing **Phytochemically Bound Trace Elements™** and other phytochemicals including polyphenolic compounds with SOD and catalase, dehydrated at low temperature to preserve associated enzyme factors.

RECOMMENDATION: Two (2) tablets one (1) to two (2) times each day as a dietary supplement or as otherwise directed by a healthcare professional.

Caution: Not recommended for pregnant or lactating women.

KEEP OUT OF REACH OF CHILDREN

Store in a cool, dry area.
Sealed with an imprinted safety seal for your protection.

NDC# 55146-03015 Rev. 5/08

ADHS® is available in bottles of 120 and 240 tablets.

For more information, contact the Client Services Department or one of our Technical Consultants at

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