

Neuroendocrine Stress Cascade and Beyond

ETI Formulas to Support Individuals During Stress*

I. Introduction

It is commonly acknowledged that a physiological function of the stress response is to coordinate autonomic, neuroendocrine, and immune reactions in the face of the possible homeostatic risks. The current allostatic model suggests "that the main role of the stress response is to mobilize the body's energy resources to promote a specific survival pattern and not necessarily maintain homeostatic systems at former levels" (Dallman et al., 2006; Nederhof & Schmidt, 2013).

This paper describes the hypothalamic-pituitary-adrenal (HPA) axis regulatory functions during stress, as well as the physiology and pathology of stressful events, followed by specific Energy Tools International (ETI) formulas and their combinations that support the brain and the body during acute and chronic stresses.

II. Stress: Physiology Facts

The findings of a number of studies conducted around the world have generated the following conclusions about stress and physiological systems: "The neuroendocrine stress cascade, containing the HPA axis, starts with the release of adrenocorticotropic hormone (ACTH) promoting substances from neurosecretory neurons in the paraventricular nucleus (PVN) of the hypothalamus" (Bruhn et al., 1984). These substances travel via portal veins to the anterior pituitary, where they can activate corticotropes with the corticotrophin-releasing factor (CRF) as the primary activator of pituitary ACTH release (Gibbs & Vale, 1982). By way of the systemic circulation, ACTH reaches the adrenal cortex and stimulates the release of glucocorticoids (Dallman et al., 1987).



From http://modaycenter.com/

Lightman et al. (2008) and Young et al. (2004) confirmed that at the adrenal, cortisol (or corticosterone) is released in pulses, the timing of which dictates the overall degree of both baseline activity and stress responses. Data show that the rhythmicity of glucocorticoid release is essential for maintaining cellular sensitivity and promotes glucocorticoid actions such as gene transcription and behavior (Conway-Campbell et at., 2010; Sarabdjitsingh et al., 2010b). Glucocorticoids then travel throughout the body, performing a mass of effects in the periphery including glycogen breakdown and gluconeogenesis (Coderre et al., 1991).

Chameau et al. (2007) and Groc et al. (2008) showed that "glucocorticoids cross the blood-brain-barrier and mostly bind to mineralocorticoid (MR) and glucocorticoid receptors (GR) in neurons and/or glia. Activation of MR increases neuronal excitability by increasing the probability of glutamate release, and increasing glutamate receptor trafficking. Activation of GR causes delayed suppression of neuronal excitability and synaptic plasticity presumably to normalize hippocampal activity after stress and protect information acquired during the stressful experience, respectively".



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According to Myers et al. (2013) all hypothalamic PVN-projecting regions receive the GABAergic and glutamatergic enter from other hypothalamic nuclei, which may be responsible for internal hypothalamic mechanisms governing the integration of forebrain limbic inputs and stress reaction based on metabolic request.

Tacker and Herman (2011) published data that the 'fast feedback' glucocorticoid effects are non-genomic in nature, acting through an endocannabinoid mechanism to inhibit glutamatergic activity.

III. Stress: Pathology Facts

Similarly, the results of numerous scientific studies conducted both in the U.S. and abroad have generated the following conclusions about stress and pathology: "The changes in biological set points that occur across the life span as a function of chronic stressors are referred to as allostasis, and the biological cost of these

adjustments is known as allostatic load" (McEwen, 1998). He has also suggested that combined rises in allostatic load are linked to chronic illness.

Immune System

Many studies confirmed that the stress-induced immune dysregulation results in significant health consequences for immune related disorders including viral infections, chronic autoimmune disease, tumor growth and metastasis (Cohen et al., 1998; Powel et al., 2013; Affleck et al., 1997; Mohr et al., 2004).

In a subsequent study of volunteers vaccinated with a cold virus, Cohen et al. (1998) observed that people with continuing chronic, stressful life events had a high possibility of catching a cold, whereas people subjected to stressful events ongoing less than a month did not.

Both human and animal studies have shown the sympathetic and neuroendocrine responses to psychosocial stress significantly impact cancer through regulation of inflammatory mediators (Powell, et al., 2013). Roitt et al. (1998) also demonstrated that the elevated basal levels of stress hormones associated with chronic stress also suppress immunity by directly affecting cytokine profiles.

In a meta-analysis of over 30 years of research, Segerstrom and Miller (2004) stated that "at the intermediate stressors, such as academic examinations, could promote a Th2 shift. A Th2 shift has the effect of suppressing cellular immunity in support of humoral immunity." In response to more chronic stressors, Segerstrom and Miller found that pro-inflammatory cytokines become deregulated and lead to suppression of both the humoral and cellular immunity.

Inflammatory state

The study by Gu, Tang and Yang (2012) demonstrated that various immunological factors are transformed under prolonged psychological stress and also cause vascular low-grade inflammation.

Research by Affleck et al. (1997) concluded that stress is associated with more swelling and reduced mobility in rheumatoid arthritis patients.

Bailey (2016) showed that exposure to different types of stressors results in the translocation of microflora from the skin and mucosal surfaces into regional lymph

nodes that might increases in inflammatory markers even in the absence of marked infection.

Diabetes

Siddiqui et al. (2015) confirmed that the chronic stress response is associated with abnormalities in glucose tolerance, insulin sensitivity and pancreatic beta cell function and risk of type 2 Diabetes Mellitus.

Brain

An exposure to stress is one of the known negative regulators of the adult neurogenesis (AN). Lucassen et al. (2015) observed the effects of acute and mild stress on AN and found that acute levels of stress can, in general, be quickly overcome, but chronic exposure can induce longer-lasting reductions in neurogenesis.

Cardio

Research by Henry et al. (1975) demonstrated that chronic central nervous system (CNS) stimulation of the cardiovascular system due to stress leads to continuous increases in blood pressure and vascular hypertrophy. "Chronically elevated blood pressure forces the heart to work harder, which leads to hypertrophy of the left ventricle. Over time, the chronically elevated and rapidly shifting levels of blood pressure can lead to damaged arteries and plaque formation" (Brownley et al., 2000).

Memory/Anxiety/Depression

Glucocorticoids have deep effects on prefrontal-mediated behaviors, including working memory, executive function, and behavioral flexibility (Barsegyan et al., 2010). "Chronic glucocorticoid signaling in the bed nucleus of the stria terminalis (BST) appears to induce a shift toward anxiogenic behavior and enhance unconditioned fear and stress-induced learning" (Ventura-Silva et al., 2012).

Several polymorphisms of the glucocorticoid receptor gene have been reported in individuals with posttraumatic stress disorder (PTSD) (Kumsta et al., 2008; van Rossum et al., 2006). It is known that the low levels of cortisol generally linked with PTSD and patients with major depression typically show hypercortisolemia (Yehuda et al., 2004).

IV. ETI Formulas to Support Individuals During Stress*

The findings cited above show the human stress response points to a reorganization of energy reserves determined by a glucocorticoid signal that pushes physiological systems to adapt, until the adaptive cost becomes greater than the adaptive capacity of the individual, with the result being "stress."

To address various aspects of stress and to reduce its negative impact on the human organism, Vital Force Technology (VFT) has developed a set of ETI formulas and has optimized their production. Given the amount of stress commonly experienced by so many people in today's world, it is no surprise these particular formulas have consistently been so popular with our customers. The VFT research data, as well as testimonials from practitioners and individuals strongly support the efficacy of ETI formulas such as Stress Relief, Balance, Foundation, Adaptogen, Master Brain, Hypothalamus Support and others for use during periods demanding high energy and resilience. The following are some benefits observed from the application of ETI formulas during acute and chronic stress conditions:

- More efficient support of the integration of multiple systems that are involved in the stress response by energetically improving cellular function, neurocircuits, and the body's overall energy production, thus decreasing the adaptive cost
- Increased precision in matching environmental requests, by shifting behavior patterns to meet anticipated needs and thereby decreasing the risk of developing a variety of stress-related pathologies
- Create additional energetic input to help the individual to generate extra adaptive capacity
- Help to return to homeostasis points, even after prolonged stress conditions.

V. Stress Decrease Formulation Based on ETI Formulas*

Formulating ETI energy patterns and their combination can be a highly skilled and creative process. Practitioners can use these specific combinations of ETI formulas, as well as fine-tune dosage, frequency and proportions of each formula, to create a personalized approach for an individual client's support during stressful conditions.

1. Fatigue, overall weakness

Description:

May help to overcome fatigue caused by frequent or sustained stress; increases energy production and engages a stable emotional state.

Formulation and Dosage:

Combined dosage of Adrenal Support (10 drops), Thyroid (5 drops) and Selenium (2-3 drops) in 2-4 oz. of water.

Drink 2-3 times per day with the last dosage no later than 2-3 hours before bed; continue up to two weeks.

Precautions: No precautions or side effects, if used with the recommended dosages.

2. Anxiety

Description:

May decrease symptoms of generalized anxiety disorder, panic disorder, and social anxiety disorder by more efficiently supporting regulation of homeostasis via HPA.

Formulation and Dosage:

Combined dosage of Adrenal Support (10 drops) with Master Brain (3 drops), Adaptogen (3 drops) and Oxytocin (2-3 drops) in 2-4 oz. of water.

Drink 2-3 times per day; increase frequency up to 5 times per day during a panic attack or severe anxiety; continue up to two weeks.

Precautions: This formulation can be very effective as an individual formulation via slight tuning of the compound's proportion. Do not use this formula during acute state of infection.

3. Depression

Description:

May be helpful with symptoms of persistent depression and seasonal affective disorder.

Formulation and Dosage:

Combined dosage of Stress Relief (5 drops), Hypothalamus Support (5 drops) and Tranquility (3-5 drops) in 2-4 oz. of water. Drink 3-4 times per day up to two weeks.

Precautions:

No precautions or side effects, if used with the recommended dosages.

4. Trauma

Description:

May help with emotional upsets, frightening memories or with a sense of constant danger.

Formulation and Dosage:

Combined Forgiveness (10 drops) with Healing Love (5 drops) in 2-4 oz. of water. Drink 2-3 times per day or when necessary.

Precautions:

No precautions or side effects, if used with the recommended dosages.

5. Mental support during stress

Description:

It can be used as a restorative tonic for the brain during stressful conditions and might help with mental fatigue, enhancement of memory and intellect.

Formulation and Dosage:

Combined Master Brain (10 drops) and Hypothalamus Support (5 drops) in 2-4 oz. of water. Drink 2-3 times per day when it is necessary, but no later than 2-3 hours before bedtime.

Precautions:

No precautions or side effects, if used with the recommended dosages.

6. Support immune system during stress

Description:

May be helpful with prolonged stressful conditions and frequent cold or flu infections.

Formulation and Dosage:

Combined Stress Relief (10-15 drops) and Acute Immune (3-5 drops) in 2-4 oz. of water. Drink up to 5 times for the first day and then 2-3 times per day up to 7-10 days.

Precautions:

No precautions or side effects, if used with the recommended dosages.

7. Support GI during stress

Description:

May be helpful with prolonged stressful conditions and compromised GI functions.

Formulation and Dosage:

Combined Stress Relief (10-15 drops) and GI Aid (3-5 drops) in 2-4 oz. of water. Drink 3 times per day up 2-3 weeks.

Precautions:

Increase the amount of water up to 4-6 oz. for individuals with GI sensitivity to minerals in the solution.

8. Support Thyroid during stress

Description:

This formula decreases the impact of stressful conditions on the thyroid gland by improving the body's capacity for adaptation.

Formulation and Dosage:

Combined Stress Relief (3-5 drops), Hypothalamus Support (3-5 drops) and Adaptogen (3-5 drops) in 2-4 oz. of water. Drink 2-3 times per day up to 2-3 weeks.

Precautions:

For those individuals with hypothyroid conditions. Use Thyroid formula to balance hyperthyroid conditions.

9. Cardio support during stress

Description:

Can be used as a restorative tonic in cases of overall weakness and might reduce the risk of heart problems during stressful conditions caused by physical overexertion and extensive exercise; may also improve body's oxygen status.

Formulation and Dosage:

Combined Heart Support (5 drops), Oxygen (3-5 drops) and Stress Relief (3-5 drops) in 2-4 oz. of water. Drink when necessary.

Precautions:

No precautions or side effects, if used with the recommended dosages.

*** Disclaimer** (i) The information is provided for educational purposes only. (ii) These statements have not been evaluated by the Food and Drug Administration (FDA). The provided information is not intended to diagnose, treat, cure or prevent any diseases or, medical problems.

References

- Dallman MF, Pecoraro NC, La Fleur SE, Warne JP, Ginsberg AB, Akana SF, Laugero KC, Houshyar H, Strack AM, Bhatnagar S, Bell ME. Glucocorticoids, chronic stress, and obesity. *Prog Brain Res*. 2006; 153:75– 105.
- Nederhof E, Schmidt M., V Mismatch or cumulative stress: toward an integrated hypothesis of programming effects. *Physiol Behav*. 2013; 106:691–700.
- 3. Bruhn TO, Sutton RE, Rivier CL, Vale WW. Corticotropin-releasing factor regulates proopiomelanocortin messenger ribonucleic acid levels in vivo. Neuroendocrinology, 1984; 39(2):170-5.
- 4. Gibbs DM, Vale W. Presence of corticotropin releasing factor-like immunoreactivity in hypophysial portal blood. *Endocrinology*. 1982; 111:1418–1420.
- Dallman MF, Akana SF, Cascio CS, Darlington DN, Jacobson L, Levine N. Regulation of ACTH secretion: variation on a theme B. Recent *Prog Horm Res.* 1987; 43:113–167.
- Lightman SL, Wiles CC, Atkinson HC, Henley DE, Russell GM, Leendertz JA, McKenna MA, Spiga F, Wood SA, Conway-Campbell BL. The significance of glucocorticoid pulsatility. *Eur J Pharmacol*. 2008; 583:255– 262.
- 7. Young EA, Abelson J, Lightman SL. Cortisol pulsatility and its role in stress regulation and health.*Front Neuroendocr*. 2004; 25:69–76.
- Conway-Campbell BL, Sarabdjitsingh RA, McKenna MA, Pooley JR, Kershaw YM, Meijer OC, De Kloet ER, Lightman SL. Glucocorticoid ultradian rhythmicity directs cyclical gene pulsing of the clock gene period 1 in rat hippocampus. *J. Neuroendocrinol.* 2010; 22:1093–100.
- 9. Sarabdjitsingh RA, Spiga F, Oitzl MS, Kershaw Y, Meijer OC, Lightman SL, de Kloet ER. Recovery from disrupted ultradian glucocorticoid rhythmicity reveals a dissociation between hormonal and behavioural stress responsiveness. *J. Neuroendocrinol.* 2010b; 22:862–71.
- Coderre L, Srivastava AK, Chiasson JL. Role of glucocorticoid in the regulation of glycogen metabolism in skeletal muscle. *Am J Physiol*. 1991; 260: E927–32.

- 11.Chameau P, Qin Y, Spijker S, Smit AB, Smit G, Joëls M. Glucocorticoids specifically enhance L-type calcium current amplitude and affect calcium channel subunit expression in the mouse hippocampus. *J. Neurophysiol.* 2007; 97:5–14.
- 12.Groc L, Choquet D, Chaouloff F. The stress hormone corticosterone conditions AMPAR surface trafficking and synaptic potentiation. *Nat. Neurosci.* 2008; 11:868–70.
- 13.Myers B, Dolgas CM, Kasckow J, Cullinan WE, Herman JP. Central stressintegrative circuits: forebrain glutamatergic and GABAergic projections to the dorsomedial hypothalamus, medial preoptic area, and bed nucleus of the stria terminalis. *Brain Struct Funct*. 2013; 219(4):1287-303.
- 14.Tasker JG, Herman JP. Mechanisms of rapid glucocorticoid feedback inhibition of the hypothalamic-pituitary-adrenal axis. *Stress*. 2011; 14:398– 406.
- 15.McEwen BS. Protective and damaging effects of stress mediators. *N. Engl. J. Med.* 1998; 338:171–179.
- 16.Cohen S, Frank E, Doyle WJ, Skoner DP, Rabin BS, Gwaltney JM., Jr Types of stressors that increase susceptibility to the common cold in healthy adults. *Health Psychol*. 1998; 17:214–223.
- 17.Powell ND, Tarr AJ, Sheridan JF. Psychosocial stress and inflammation in cancer. *Brain Behav Immun*. 2013; 30:S41-7.
- 18.Affleck G, Urrows S, Tennen H, Higgins P, Pav D, Aloisi R. A dual pathway model of daily stressor effects on rheumatoid arthritis. Ann. Behav. Med. 1997; 19:161–170.
- 19.Mohr DC, Hart SL, Julian L, Cox D, Pelletier D. Association between stressful life events and exacerbation in multiple sclerosis: a meta-analysis. *Br. Med. J.* 2004; 328:731.
- 20.Roitt I, Brostoff J, Male D. *Immunology*. 5th ed. London: Mosby Int.; 1998. p. 125.
- 21.Segerstrom SC, Miller GE. Psychological stress and the human immune system: a meta-analysis of 30 years of inquiry. *Psychol. Bull.* 2004; 130:601–630.
- 22.Gu HF, Tang CK, Yang YZ. Psychological stress, immune response, and atherosclerosis. *Atherosclerosis*. 2012 Jul;223(1):69-77.
- 23.Bailey, MT., 2016. Psychological Stress, Immunity, and the Effects on Indigenous Microflora. *Adv Exp Med Biol*. 2016; 874:225-46.
- 24. Siddigui A, Madhu SV, Sharma SB, Desai NG. Endocrine stress responses and risk of type 2 diabetes mellitus. *Stress*. 2015;18(5):498-506

- 25. Lucassen PJ, Oomen CA, Naninck EF, et al. Regulation of Adult Neurogenesis and Plasticity by (Early) Stress, Glucocorticoids, and Inflammation. *Cold Spring Harb Perspect Biol*. 2015; 1:7(9).
- 26.Henry JP, Stephens PM, Santisteban GA. A model of psychosocial hypertension showing reversibility and progression of cardiovascular complications. *Circ. Res.* 1975; 36:156–164.
- 27.Brownley KA, Hurwitz BE, Schneiderman N. Cardiovascular psychophysiology. In: Cacioppo JT, Tassinary LG, Berntson GG, editors. *Handbook of Psychophysiology*. 2nd ed. New York: Cambridge Univ.; 2000. pp. 224–264.
- 28.Barsegyan A, Mackenzie SM, Kurose BD, McGaugh JL, Roozendaal B. Glucocorticoids in the prefrontal cortex enhance memory consolidation and impair working memory by a common neural mechanism. *Proc. Natl. Acad. Sci. U. S. A.* 2010; 107:16655–60.
- 29.Ventura-Silva AP, Pêgo JM, Sousa JC, Marques AR, Rodrigues AJ, Marques F, Cerqueira JJ, Almeida OFX, Sousa N. Stress shifts the response of the bed nucleus of the stria terminalis to an anxiogenic mode. *Eur. J. Neurosci.* 2012; 36:3396–406.
- 30.Kumsta R, Entringer S, Koper JW, van Rossum EFC, Hellhammer DH, Wüst S. Glucocorticoid receptor gene polymorphisms and glucocorticoid sensitivity of subdermal blood vessels and leukocytes. *Biol. Psychol.* 2008; 79:179–84.
- 31.Van Rossum EFC, Binder EB, Majer M, Koper JW, Ising M, Modell S, Salyakina D, Lamberts SWJ, Holsboer F. Polymorphisms of the glucocorticoid receptor gene and major depression. *Biol. Psychiatry*. 2006; 59:681–8.
- 32.Yehuda R, Halligan SL, Golier JA, Grossman R, Bierer LM. Effects of trauma exposure on the cortisol response to dexamethasone administration in PTSD and major depressive disorder. *Psychoneuroendocrinology*. 2004; 29:389–404.