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ADAPTOGENS

Introduction and Overview

The following is a discussion of adaptogens, including history, definition, and criteria for inclusion. Stress and the stress response will be discussed, including information on homeostasis, the H-P-A axis and the more modern concept of allostasis. All of this is important when referencing adaptogens, as they are key plants to consider when a person is in an acute or chronically hyperaroused state from stress or the perception of stress.

History of Adaptogens

In 1947, N.V. Lazarev, a pharmacologist, was the first to use the term adaptogen to describe the unexpected effects of an arterial dilator developed in France, dibazol (2-benzylbenzimidazol) (Panossian et al, 1999). Lazarev discovered that dibazol increased the resistance of organisms to stress (Panossian et al, 1999). Dibazol was found to be effective in medication for damage to different regions of the nervous system and to increase non-specific resistance to adverse influences. This new group of medicinal substances contributed to "a state of nonspecifically increased resistance" or SNIR of the organism. These medicinal substances that caused SNIR were named "adaptogens". (Brekhman et al, 1968)

Approximately 35-40 years ago, the former USSR conducted much research on adaptation and stress and the mechanism of action in such situations as high-altitude hypoxia, physical load training, with emphasis on finding ways to increase adaptation in a number of highly stressful situations, seeking to develop methods and pharmacological agents that would help humans to ultimately adapt and cope. (Panossian et al, 1999). In the USSR the study of adaptogens actually morphed into a field of biomedicinal research, specifically targeting stress research, and mapping or screening biologically active substances of natural origin, mainly from plants (Panossian et al, 1999)

Although in 1947 Lazarev first coined the term adaptogen, traditional medicine has been using plants for these adaptogenic purposes for a long time (Brekhman et al, 1968). Tonic plants are some of the most ancient medicinal remedies of folk medicine in many parts of the world and in many different cultures. Brekhman and colleagues analyzed 158 complex prescriptions of folk medicine in different Asian countries and found 116 of these included plants of tonic action (Brekhman et al, 1968). They chemically analyzed the plants and found that glycosides were prevalent in these tonic plants, as well as alkaloids in a smaller percentage of cases. In looking at the current and past use of these plants in folk medicine, they found that corroborative action was prevalent in treatment for hypertension, atherosclerosis, diabetes, cancer, tuberculosis, anemia and other diseases. (Brekhman et al, 1968)

General Adaptation Syndrome

When stress is discussed in these works, it is used as defined by Hans Selye's theory about stress, which is defined as a state of threatened homeostasis. In 1936, Selye conducted experiments on rats and found that various stressors (cold, heat, noise, chemicals, etc.) induced the same "non-specific" generalized physiological response of the organism (stomach and colon ulceration, atrophy of immune system tissue and increase of adrenals) – he named this 'stress'. (Panossian et al, 1999).

Selye identified three phases of an organism's stress response (McCance, 2004).

1. First is the alarm phase, when a stimulus triggers the body's stress response system. Activation of the Sympathetic Nervous System results in increased secretion of epinephrine and norepinephrine. These stress hormones prepare the body for 'flight or fight'. Attention and memory are heightened, as well as problem-solving skills. The Hypothalamus-Pituitary-Adrenal (HPA) axis directs the adrenal glands to secrete more cortisol. Cortisol, another stress hormone, directs the body to increase energy by released stored fat as triglycerides, converting stored energy to glucose and breaking down proteins. (McCance, 2004) (Spelman, 2004) (Brown and Gerbarg, 2004)
2. Second phase is the resistance phase. If a stressor continues, the damaged cells from the alarm phase are repaired and rebuilt via anabolism, which also prepares the body for future stressors. (McCance, 2004) (Brown and Gerbarg, 2004)
3. Third phase is the exhaustion phase (McCance, 2004), which happens when the stressor continues beyond the body's capacity to resist it (Brown and Gerard, 2004). It is in this phase where continual stress leads to breakdown and depletion of homeostasis (Spelman, 2004) and breakdown of compensatory mechanisms (McCance, 2004). Per Selye, this phase is considered the most detrimental to health and marks the onset of certain diseases (McCance, 2004).

Selye referred to these three phases as the General Adaptation Syndrome. These phases describe a stereotypic non-specific response to stressor signals from variable sources. This adaptation response gives an organism the ability to resist against stressors and to adapt to environmental challenges and changes. Selye ascertained that the factor limiting adaptability was the organisms 'adaptation energy', which is the capacity of the organism to resist adverse environmental influences. This capacity is finite and declines with increasing and or continuous exposure to stressors. Faulty adaptation leads to disease. (Wagner et al, 1994)

The Stress Response

Stress is simply a fact of nature as all organisms are constantly interacting with their environments (external and internal), both physically and behaviorally. In stress a demand exceeds a person's ability to cope, with the result being disturbances of cognition, emotion, and behavior which can adversely impact well-being (McCance, 2004). Stressors come in a variety of forms including

environmental (heat, cold, radiation), chemical (pesticides, pollutants, free radicals and other waste products of metabolism), biological (bacteria and viruses) and /or psychological (a major life event such as divorce or death or a loved one, job loss, etc., socioeconomic status (Spelman, 2004) (Brown and Gerard, 2004). Many studies show clearly that negative stressors produce biological changes in almost all systems of the body, and a complex chain of biological and psychological processes are involved (Syvalahti, 1987).

If the brain perceives any stimuli as a cause for alarm, the stress response system is activated (McCance, 2004), including activation of the sympathetic branch of the autonomic nervous system and the Hypothalamus-Pituitary-Adrenal axis (HPAA) (McCance, 2004). The HPAA refers to our neuroendocrine system, which is one of our major auto-regulatory systems and consists of seven small glands. The HPAA is able to sense what is going on within and around us and then prioritize how our limited energy should be directed. (Yance, 2005) (McCance, 2004) The neuroendocrine network is a very complex, integrated system, replete with feedback control mechanisms, and an overriding control of the whole system by internal biological rhythms or external events impacting the hypothalamus (Syvalahti, 1987).

The balance of the HPAA is critical to optimum health. Over time, if an organism is under prolonged stress conditions, hormone balance is shifted towards a catabolic process of constantly shifting to release more stress hormones in order to attempt to adapt to the stressful situation. (Yance, 2005). Profound changes may occur in the secretory patterns of hormones (Syvalahti, 1987). This shifting of hormones is detrimental to health as it causes more oxidative damage and lowers the levels of anabolic hormones needed for building up. As a result, the whole endocrine system is thrown out of balance (including the thyroid, pancreas, reproductive, thymus, etc.). Anabolic metabolism determines muscle mass, influences immunity, protein synthesis, cell proliferation, bioenergetics, cell communication, endocrine function, and of course mind, mood and behavior. (Yance, 2005)

While the sympathetic nervous system is upregulated, the parasympathetic nervous system is downregulated, thus allowing all energies to be diverted to the need to ‘fight or flight’. The body is amazingly prepared to deal with such emergency situations so that when there is an acute danger, all body systems rally and coordinate to protect vital processes and systems. Once the threat or perceived threat is gone, then under normal conditions, the body returns to a balanced state, whereby the maintenance of homeostasis or stability through change is maintained. This maintenance of stability through change is called allostasis (McEwen, 1999).

The problem occurs when the body is in a constant state of hyperarousal, which occurs frequently in our modern day society. The body is not equipped to deal with being constantly in the fight or flight mode, and after chronic hyperarousal, systems start breaking down, as being chronically aroused comes at a metabolic expense and uses critical organ reserve (Spelman, 2004). When the body is constantly trying to fight the tiger because it is constantly stressed, be it real or

perceived, then what energy is normally reserved to keep the set points in a set range and in homeostasis or allostasis, is now being sacrificed to fight the enemy. There is a wear and tear exacted on the body, also called allostatic load, as the body is constantly trying to achieve allostasis (McEwen, 1999). An example of this is when the body is constantly secreting high levels of cortisol and catecholamines, and becomes less efficient in turning on or shutting off these stress responses (McEwen, 1999). The HPAA system becomes dysregulated, resulting in a constant secretion of cortisol (Spelman, 2004) and other hormones/neurotransmitters. Organ reserve is being depleted. Organ reserve includes protein synthesis, blood flow, and mitochondria. Loss of organ reserve includes a loss of enzyme activity (due to loss of enzyme protein) as well as loss of activity of the respiratory chain that occurs during aging (Spelman, 2004). The loss of the respiratory chain may be responsible for the loss of skeletal and heart muscle that occurs often during aging (Spelman, 2004). Deletions of the mitochondrial genome have been found in the aged human tissue in the skeleton, myocardium, brain, external eye muscles, liver and more (Spelman, 2004). Often the enemy is a function of our own decisions on lifestyle, nutrition, reaction to life, etc.

The sharper, keener problem-solving skills that occur in acute stress actually dull during Selye's exhaustion stage mentioned above. Prolonged stress also often results in depression and anxiety; sleep disorders, dysrhythmia, chronic headaches, backaches, maladaptive coping behavior (i.e. overworking, hyperactivity, overeating) and hypertension to name a few (Spelman, 2004).

The short-term effects of glucocorticoid hormones include inhibition of sexual motivation, regulation of the immune system, increased gluconeogenesis, and increased foraging behavior. Long-term adaptation results in inhibition of reproduction, suppression of the immune system, promotion of protein loss, and suppression of growth (Spelman, 2004).

Adaptogens Defined

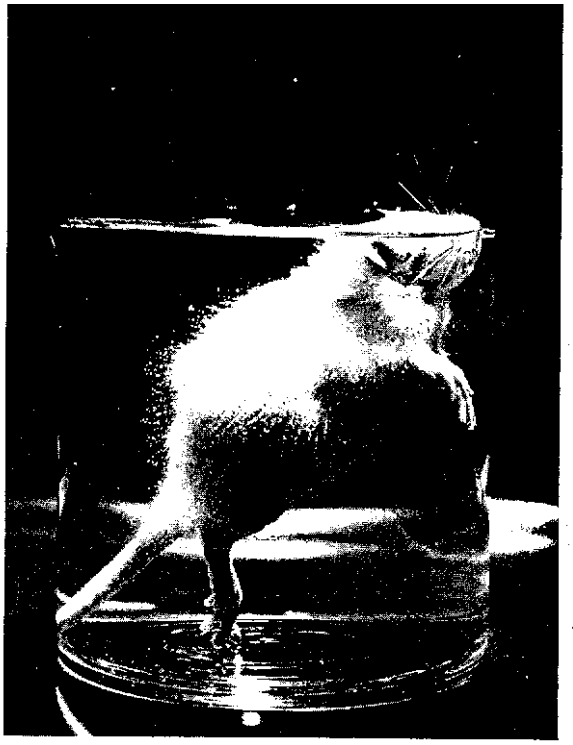
Brekhman and Dardymov studied adaptogenic plants and further defined the term adaptogen as follows:

1. An adaptogen must be innocuous, and cause minimal disorders in the physiological functions of an organism (Brekhman et al, 1968). It must not influence normal body functions more than required (Wagner et al, 1994).
2. The action of an adaptogen should be nonspecific, i.e. it should increase resistance to adverse influences of a wide range of physical, chemical and biological factors (Brekhman et al, 1968).
3. An adaptogen may possess normalizing action independent of the nature or direction of the pathologic changes or state (Brekhman et al, 1968) (Wagner et al, 1994). If a body parameter is high, the adaptogen brings the parameter towards normal; if it is low, the adaptogen tends to bring it up towards normal (Brown et al, 2002).

Adaptogens tend to reinforce the non-specific power of resistance against stressors, increase overall capacity to manage situations of stress, and protect against disease caused by overstress (Wagner et al, 1994). In their studies of

adaptogenic plants, Brekhman and Dardymov found that Rhodiola rosea, along with P. Ginseng, Eleutherococcus senticosus and Raponticum carthamoides contributed to a more sparing use of carbohydrates and to increased resynthesis of glycogen and high-energy phosphorus compounds (Brekhman et al, 1968). This action was apparent during physical strain. The results also showed an anabolic action as shown with increases of body weight, restoration of blood albumin after massive bleeding, and on immune system enhancement.

One of the more important actions of adaptogens noted by Brekhman was the capacity of adaptogens, including Rhodiola rosea, to increase efficiency both after a single (stimulant action) or prolonged (tonic action) administration. The difference between the stimulant actions of the plant preparations used and Benzedrine-like compounds was that the plants had low toxicity and no pronounced excitant action. The plants also didn't lead to sleep problems, either falling asleep or waking in the middle of the night. (Brekhman et al, 1968) In more recent research, after a single dose, Rhodiola rosea was found to be more active than the adaptogens Schizandra chinensis and Eleutherococcus senticosus, producing within 30 minutes of intake a stimulating effect that continued for 4-6 hours (Panossian and Wagner, 2005).



In 1978, Roger Porsolt and other Russian scientists developed a forced swimming test to measure nonspecific resistance to stress. The Porsolt test involved a mouse or rat being forced to swim to exhaustion (approximately 15 minutes). The rodent would initially frantically try to stay afloat, and after this initial period, would adopt a characteristic immobile posture (one I've seen often in humans!), making only the most minimal movements to stay alive and above water. Refer to the picture of the rat for this characteristic posture of immobility after 10 minutes immersion in water (Porsolt et al, 1978) This test initially became a screening test for antidepressants by pharmaceutical companies (Brown et al, 2002).

Adaptogens and antidepressants have been found to increase the duration of time that rats are able to keep swimming actively (Brekhman et al, 1968) (Brown et al, 2002). Brekhman found that in stress, adaptogens may actually increase nonspecific resistance rather than lessen it. They did an experiment where two groups of rats were made to swim in water. Eleutherococcus (0.2 ml/g) was injected intraperitoneally into one half of the rats. After five hours half of the rats were killed, and a comparison of the adrenals was made. In comparing the

adrenals of rats that were not made to swim, a five-hour swimming caused marked hypertrophy of the adrenals in the controls, which was almost completely prevented with the Eleutherococcus treated group. There was a clear anti-alarm action seen with the Eleutherococcus extract, and increased resistance, as the treated rats were able to swim 52 minutes longer (9.2%) until complete fatigue (death). (Brekhman et al, 1968)

Brekhman also observed a number of effects of these plant adaptogens on the cell. Many of the effects noted were anabolic (influencing the processes of biosynthesis of protein and nucleic acids, including stimulating the production of immune bodies) and protective. Many of the plants studied showed antioxidant action, including Rhodiola rosea. (Brekhman et al, 1968)

Adaptogens and the Stress Response

As elucidated earlier, through various studies of plant adaptogens, Brekhman showed that adaptogens have the ability to regulate the stress response in a variety of ways. Adaptogens are considered a new class of natural, metabolic regulators which have been shown through repeated studies to increase the ability of an organism to adapt to and avoid damage from environmental stressors (Panossian et al, 1999). The adaptogenic effect is seen to increase the basal level of dynamic equilibrium (homeostasis) (Panossian et al, 1999) or allostasis (McEwen & Seeman, 1999) of switch on and off systems, including activators NO, PAF, and catecholamines and such inhibitors as cortisol and PGE_2 (Panossian et al, 1999). Adaptogens affect many regulatory systems in the organs and tissues, such as the immune, hormonal, Central Nervous System, cardiovascular, and muscular systems (Brown et al, 2002). Adaptogens alter the systems' reactivity to stress, i.e. the defense system, including the HPA axis and the Sympatho-adrenal system (SAS) (Brown et al, 2002) (Panossian et al, 1999). In this way, adaptogens may reduce the damage from stressors, including the HPA axis and the SAS (Panossian et al, 1999).