

## Stress response

By Dr. Nicholas Larkins

### The stress response can have a major impact on health.

Stress response has been described as the consequence of the failure of an organism – human or animal – to respond appropriately to emotional or physical threats, whether actual or imagined. (Selye H, History of the Stress Concept. in Goldberger L, Breznitz S. Handbook of Stress: Theoretical and Clinical Aspects. Free Press, 1982)

Stress symptoms can commonly include a state of alarm and adrenaline production, short-term resistance as a coping mechanism, and exhaustion, as well as irritability, muscular tension, inability to concentrate and a variety of physiological reactions such as headache and elevated heart rate. This can cover a wide range of phenomena, from mild irritation to drastic dysfunction that may cause severe health breakdown.

Signs of stress may be cognitive, emotional, physical or behavioural. Signs include poor judgment, a general negative outlook, excessive worrying, moodiness, irritability, agitation, inability to relax, feeling lonely, isolated or depressed, aches and pains, diarrhoea or constipation, nausea, dizziness, chest pain, rapid heartbeat, eating too much or not enough, sleeping too much or not enough, social withdrawal, procrastination or neglect of responsibilities, increased alcohol, nicotine or drug consumption, and nervous habits such as pacing about or nail-biting.

### General adaptation syndrome

Stress is how the body reacts to a stressor, real or imagined, a stimulus that causes stress. Acute stressors affect an organism in the short term; chronic stressors over the longer term.

The stress response is actually composed of two interrelated systems.

The first, the catecholamine-mediated system is controlled by two primary hormones: epinephrine and norepinephrine. These systems are commonly known as the sympathetic or 'fight and flight' system prepares the body to act.

The second the hypothalamic-pituitary-adrenal axis is mediated primarily by cortisol which mobilises energy (McCance KL and Shelby J, Stress and Disease. Pathophysiology: the biological basis for disease in Adults, 2nd edition, Mosby, St Louis, 1994, pp. 299-322., Michelson D et al., Mediation of the stress response by the hypothalamic-pituitary-adrenal axis in Friedman MJ et al. Eds in Neurobiological and Clinical Consequence of Stress Lippincott-Raven, Philadelphia, 1995, pp.225-238)

A paramount goal of the stress response is to maintain glucose levels. When functioning correctly the stress response is quite efficient at maintaining serum glucose levels that optimise health.

However when the system malfunctions, it will err by promoting an elevation of glucose levels rather than risking the potential disaster of a low glucose supply. (Ober KP. Alterations in fuel metabolism in critical illness Endocrinology of Critical Diseases Human press, Totowa NJ, 1997, p.p 211-232)

In this instance the stress response becomes a potent destructive, catabolic force mediated by a vicious circle of elevated glucocorticoids, insulin hypersecretion and insulin resistance. Whether the stress response will be adaptive or maladaptive depends upon its ability to shut itself down when the danger has passed. (McEwan BS. Adrenal steroid actions on brain: Dissecting the fine line between protection and damage in neurobiological and Clinical Consequences of Stress in Neurobiological and Clinical Consequence of Stress Lippincott-Raven, Philadelphia, 1995, pp135-147)

The ability to successfully shut down depends on a receptor mediated negative feedback loop which can be neutralised with great effectiveness by chronically elevated cortisol (Meaney MJ et al.. Early environment and the development of individual differences in the hypothalamic-pituitary-adrenal stress response, in Pfeffer CR, ed, Severe Stress and mental Disturbance in Children. American Psychiatric press, Washington DC, 1996, pp. 85-130)

### **Why would cortisol be elevated?**

Consider the following list of potential inducers of cortisol secretion - most of which may be encountered on an almost daily basis:

- Infection
- Noise
- Decreased and/or poor quality oxygen supply (airplane/shopping malls, clubs, a/c ....)
- Pain
- Malnutrition -lacking conditionally essential ingredients in the diet (eg: a McDonalds' diet)
- Heat
- Cold
- Trauma
- Old age
- Drugs - including medically prescribed drugs
- Obesity (metabolic syndrome)
- Disease
- Surgical interventions
- Responses to life events

Responses to life events (which could include any or all of the above) has been included because stressors do not require the physical presence of 'something' to induce cortisol secretion.

The perception of stress can be and is a powerful inducer. (LeDoux JE. Setting 'stress' into motion: brain mechanisms of stimulus evaluation, in Neurobiological and Clinical Consequence of Stress Lippincott-Raven, Philadelphia, 1995, pp. 125-134)

## **Why does the stress response contain biochemical mechanisms that can be so destructive when functioning in a maladaptive manner?**

This might be best answered by using an analogy of a caveman when he/she encountered a sabre-toothed tiger. Most of the resulting physiologic pathways involved would be typical of those triggered in our present-day human populations.

While the following key aspects of the stress response seem primarily destructive in the context of modern society they were quite helpful in promoting the survival of the caveman.

### **Elevation of Serum Glucose**

The caveman had to first decide that danger existed and then determine the best course of action with extreme rapidity.

This activity requires proper brain function - a process that requires glucose.

He/she had to make an appropriate physical action. This requires increased cardiovascular tone and respiration - again fuelled by glucose.

### **Where would all this glucose come from?**

The first thought might be storage depots. However the human is unable to store glucose with the exception of small amounts in the form of glycogen.

Another possibility would be to eat a glucose producing food such as an apple before starting the escape process - but taking time to do so would be a fatal error in this instance.

Therefore since glucose cannot be stored to any meaningful extent and since taking time to eat is inherently self-destructive something within our caveman must be converted to glucose almost instantaneously in order to ensure escape.

Since fat is stored in large quantities in adipose tissue it would appear to be the logical choice of a substance to be converted. Fat, however, cannot be converted into glucose (Coffee CJ. Metabolism, First Edition, fence creek Publ., Madison CT, 1998, pp. 101-109).

This leaves protein as the only substance that exists in adequate quantities to fuel the escape process by its conversion to glucose. Thus, in the stress response, protein catabolism is greatly increased while the resulting amino acids are converted into sugar in the process of gluconeogenesis (Matthews DE and Battezzati A. Substrate kinetics and catabolic hormones, in Kinney JM and Tucker HN, eds. Organ Metabolism and Nutrition: ideas for Future Critical care. Rave Press, New York, 1994, pp. 1-22)

### **Gluconeogenesis**

The major sources of protein for catabolism are muscle and gut (Leverve XM. Amino acid metabolism and gluconeogenesis in Cynober LA, ed. Amino Acid metabolism and Therapy in health and Nutritional Diseases. CRC Press, Boca Raton, 1995, pp.

45-56). While these sources are less than ideal they make sense because the stress response is a biomechanical compromise during which the body uses whatever resources are available in order to gain an advantage over immediate danger..

Thus during physiologic stress long-term health is sacrificed in order to ensure short term survival.

While gluconeogenesis primarily involves the conversion of protein to glucose it also includes other less dominant glucose-forming pathways. One of these which again may compromise long-term health is enhanced conversion of pyruvate to lactate (Mizock BA. Alterations in carbohydrate metabolism during stress: a review of the literature *Am J med* 98:75, 1995)

Under ideal circumstances pyruvate is converted to acetylCoA which in turn is converted to ATP via the Krebs (Citric acid) cycle.

The stress response, however, takes advantage of the ability of lactate to be converted to glucose in a process known as the Cori Cycle. ( Van Cromphaut SJ. Hyperglycaemia as part of the stress response: the underlying mechanisms. *Best Pract Res Clin Anaesthesiol.* 2009 Dec;23(4):375-86., Mizock BA. The multiple organ dysfunction syndrome. *Dis Mon.* 2009 Aug;55(8):476-526., Mizock BA. Alterations in fuel metabolism in critical illness: hyperglycaemia. *Best Pract Res Clin Endocrinol Metab.* 2001 Dec;15(4):533-51. )

While this results in a higher production of glucose, lactate - a muscle irritant - is increased. Energy-efficient aerobic metabolism is sacrificed in favour of energy-inefficient anaerobic glycolytic metabolism. This process, which has been called the futile cycling of carbohydrate may help to explain why fatigue and achy muscles are so common in those with chronic maladaptive immune responses. (Fish JA. *Metabolic Stress. Contemporary Nutrition Support practice: A Clinical Guide.* Saunders Co., Philadelphia, 1998, pp. 539-546)

Increased lipolysis is a third aspect of gluconeogenesis that provides approximately 20% of the glucose production of stress. Fats are composed of fatty acids attached to a backbone of glycerol. Glycerol can be converted to glucose. Moreover some fat can still be converted to ATP via the Krebs cycle and the ATP then can fuel the engine of gluconeogenesis by promoting the activity of three key gluconeogenic enzymes. In the long term this fat loss is far from uniform and often causes increased visceral fat accumulation ( Björntorp P, Rosmond R. The metabolic syndrome--a neuroendocrine disorder? *Br J Nutr.* 2000 Mar;83 Suppl 1:S49-57., Björntorp P. Heart and soul: stress and the metabolic syndrome. *Scand Cardiovasc J.* 2001 Jul;35(3):172-7)

## **Insulin Resistance**

For the caveman to successfully escape the sabre-toothed tiger it is not enough to just produce more glucose.

A mechanism must also exist that ensures that the glucose is preferentially directed to the systems that are most vital to the escape process.

This is accomplished by producing a state of insulin resistance (Matthews DE and Battezzati A. Substrate kinetics and catabolic hormones, in Kinney JM and Tucker HN, eds. Organ Metabolism and Nutrition: ideas for Future Critical care. Rave Press, New York, 1994, pp. 1-22)

The function of insulin is to facilitate entry of glucose into insulin-sensitive tissues. By creating a state of insulin resistance the stress response assures that glucose will only be used by tissues that utilize glucose without the aid of insulin namely those that are most vital to the escape process - such as the brain resistance (Little RA et al., Insulin Resistance and tissue fluids in Kinney JM and Tucker HN, eds. Organ Metabolism and Nutrition: ideas for Future Critical care. Rave Press, New York, 1994, pp. 49-68)

Thus insulin resistance may be a short term compromise to assure short term survival (Björntorp P, Holm G, Rosmond R. Neuroendocrine disorders cause stress-related disease. "Civilization syndrome" is a growing health problem. Lakartidningen. 1999 Feb 24;96(8):893-6., Björntorp P. Body fat distribution, insulin resistance, and metabolic diseases. Nutrition. 1997 Sep;13(9):795-803.,)

### **Suppression of Nonessential Functions**

To successfully escape the sabre toothed tiger the caveman must funnel tremendous amounts of energy to key systems in an extremely rapid manner. Therefore many many functions considered to be non-essential or even detrimental to the escape process are downregulated. (Stratakis CA, Chrousos GP. Neuroendocrinology and pathophysiology of the stress system. Ann N Y Acad Sci. 1995 Dec 29;771:1-18)

Sleep: because of the serious danger caused by fatigue: sleep inducing mechanisms are suppressed . ( Michelson D et al., Mediation of the stress response by the hypothalamic-pituitary-adrenal axis in Friedman MJ et al. Eds in Neurobiological and Clinical Consequence of Stress Lippincott-Raven, Philadelphia, 1995, pp.225-238., Vgontzas AN, et al., Chronic insomnia and activity of the stress system: a preliminary study. J Psychosom Res. 1998 Jul;45(1 Spec No):21-31.)

Feeding: if the caveman instinctively responded to hunger pangs and stopped to eat an apple - he/she would become the tiger's next meal.

Reproduction: counterproductive behaviour - the elevated cortisol suppresses the production of the major reproduction hormones. (Kudielka BM, Wüst S. Human models in acute and chronic stress: assessing determinants of individual hypothalamus-pituitary-adrenal axis activity and reactivity. Stress. 2010;13(1):1-14.)

Growth: as the anabolic processes necessary for growth are irrelevant for escape production of both growth hormone and insulin-like growth factor-1 (GF-1) are down regulated by cortisol.(Stratakis CA, Gold PW, Chrousos GP. Neuroendocrinology of stress: implications for growth and development. Horm Res. 1995;43(4):162-7)

### **Modification of metabolic rate and Immune Function**

The tremendous demands of the stress response lead to an overall increase in metabolic rate (Matthews DE). However this increase comes at a cost. This process is catabolic in nature and leads to the loss of many vital tissues particularly those that are protein based.

In fact this process has been described as 'autocannibalism' (Fish JA. Metabolic Stress. Contemporary Nutrition Support practice: A Clinical Guide. Saunders Co., Philadelphia, 1998, pp. 539-546., Ross RJ, Miell JP, Buchanan CR. Avoiding autocannibalism. BMJ. 1991 Nov 9;303(6811):1147-8)

To help counterbalance the loss of protein caused by the hyper-metabolic state the body employs an ingenious device during the stress response: thyroid function is downregulated (Spencer CA, et al., Detection of residual and recurrent differentiated thyroid carcinoma by serum thyroglobulin measurement. Thyroid. 1999 May;9(5):435-41)

This process can be described as euthyroid sick syndrome (LoPresti JS et al.s Thyroid Response to Critical illness, in Ober KP ed. Endocrinology of Critical Diseases Humana Press, Totowa, NJ, 1997, pp. 155-173). All the major diagnostic indicators of thyroid function (TSH, T3, T4) will demonstrate low thyroid function even though the gland itself demonstrates no physical evidence of ill health. (This begs the question. Is hypothyroidism better treated by stress physiology mechanisms than by hormone replacement?)

One well known result of chronically elevated glucocorticoid levels is suppression of immunity. However during the stress response the effects of cortisol are not uniform ((McCance KL and Shelby J, Stress and Disease. Pathophysiology: the biological basis for disease in Adults, 2nd edition, Mosby, St Louis, 1994, pp. 299-322).

Specific mediators of systemic immunity such as immunoglobulins, lymphocytes, eosinophils, kinins, prostaglandins, and histamines are suppressed – at least initially. In contrast the quantity of the primary mediator of local immunity such as polymorphonuclear leukocytes are increased.

### **Why might this occur?**

Again consider the analogy of the caveman and the sabre tooted tiger. What if while running the caveman injured him/herself tripping over and was actually bitten by the tiger but was still managed to escape?

In such a situation it is important to have a mechanism that would quickly halt the bleeding and also be able to prevent infection – both of which can be accomplished by increasing polymorphonuclear lymphocytes.

In such a situation it would be counterproductive to develop the effects of systemic inflammation: fever, malaise, achy muscles. Consequently the production of the normal mediators of systemic immunity (lymphocytes, eosinophils, kinins, prostaglandins and histamines) are suppressed. Unfortunately this down-regulating effect is somewhat short lived. Eventually prolonged inflammation – such as is seen in autoimmune conditions such as rheumatoid arthritis, ankylosing spondylitis,

diabetes - can lead to glucocorticoids resistance by reducing glucocorticoids receptor binding affinity (Torpy DJ, Chrousos GP. General adaptive syndrome> an overview, in Ober KP ed. Endocrinology of Critical Diseases Humana Press, Totowa, NJ, 1997.pp. 1/24). This results in a heightened pro-inflammatory response, primarily through increased cytokine production (Moldawer LL and Lowry SF Interactions among inflammatory cytokine and the classic macroendocrine system in sepsis and inflammation, organ metabolism and Nutrition: ideas for future critical care raven press, NY, 1994, pp 119-136., Seok J, Moldawer LL, A dynamic network of transcription in LPS-treated human subjects. BMC Syst Biol. 2009 Jul 28;3:78)

## Blood Volume

Another important function of the stress response is the maintenance of the proper blood volume. Consider again our troubled friend - the caveman. In order to facilitate escape increased levels of blood must get to key organs such as the heart and lungs. To accomplish this elevated cortisol signals and increase in the production of the mineralocorticoids: aldosterone and antidiuretic hormone ((Fish JA. Metabolic Stress. Contemporary Nutrition Support practice: A Clinical Guide. Saunders Co., Philadelphia, 1998, pp. 539-546). This in turn, alters renal filtration mechanic so that sodium and bicarbonate are retained and increased levels of potassium and magnesium (Fish JA. Metabolic Stress. Contemporary Nutrition Support practice: A Clinical Guide. Saunders Co., Philadelphia, 1998, pp. 539-546), Quamme GA. Molecular identification of ancient and modern mammalian magnesium transporters. Am J Physiol Cell Physiol. 2010 Mar;298(3):C407-29. Epub 2009 Nov 25., Dai LJ, Ritchie G. Magnesium transport in the renal distal convoluted tubule. Physiol Rev. 2001 Jan;81(1):51-84.) are excreted. The net result is water retention which can then enable maintenance of blood volume. This begs the question: could essential hypertension be nothing more than a loss of homeostatic control of the stress response?

## Nutrient Depletion

Several important nutrients undergo significant depletion during the stress response. These include:

- Magnesium and potassium: both are significantly depleted due to losses in the urine (Fish JA. Metabolic Stress. Contemporary Nutrition Support practice: A Clinical Guide. Saunders Co., Philadelphia, 1998, pp. 539-546), mme GA. Recent developments in intestinal magnesium absorption. Curr Opin Gastroenterol. 2008 Mar;24(2):230-5.)
- Glutamine: due to its conversion to alanine and glucose during stress-mediated gluconeogenesis (Sakiyama T, Musch MW. Glutamine increases autophagy under Basal and stressed conditions in intestinal epithelial cells. Gastroenterology. 2009 Mar;136(3):924-32. Epub 2008 Dec 3., Tjader I et al., Exogenous glutamine--compensating a shortage? Crit Care Med. 2007 Sep;35(9 Suppl):S553-6.) glutamine can be depleted by up to 50%.

- Carnitine: due to the increased rate of lipolysis during stress carnitine levels can be significantly depleted (Bahl JJ, Bressler R. The pharmacology of carnitine. *Annu Rev Pharmacol Toxicol*. 1987;27:257-77., Kizhakekuttu TJ, Widlansky ME. Natural Antioxidants and Hypertension: Promise and Challenges. *Cardiovasc Ther*. 2010 Mar 29)
- Vitamin C, Zinc and CoEnzyme Q10: due to hyper- metabolism higher levels of these nutrients may be required (Haleng J et al., Oxidative stress. *Rev Med Liege*. 2007 Oct;62(10):628-38., Wilburn AJ et al., The natural treatment of hypertension. *J Clin Hypertens (Greenwich)*. 2004 May;6(5):242-8., Werbach MR. Nutritional strategies for treating chronic fatigue syndrome. *Altern Med Rev*. 2000 Apr;5(2):93-108., Chen H, Tappel AL. Vitamin E, selenium, trolox C, ascorbic acid palmitate, acetylcysteine, coenzyme Q, beta-carotene, canthaxanthin, and (+)-catechin protect against oxidative damage to kidney, heart, lung and spleen. *Free Radic Res*. 1995 Feb;22(2):177-86)

## Clinical Implications

Why would a process that is so destructive exist in the first instance?

Perhaps the world of our caveman was primarily benevolent – as a consequence the stress response would only be activated on rare occasions. Eventually it would be hoped that our cavemen would escape the sabre toothed tiger allowing him/her to eat, to sleep, to recuperate, to reproduce.

By contrast – how many of those in today’s chronically stressed environments ever truly escape from those ‘sabre toothed tigers’ that seem to be endlessly chasing us? Our ‘sabre toothed tigers’ appear in all shapes and forms. These days we can illustrate our ‘sabre toothed tiger’ with that ever-present word ‘stress’ and all that it entails. Given that stress responses can be triggered by a perception of danger even though no actual danger exists and given that “stressed out” has become a popular expression in modern society.

When a person’s perception to the world is transformed from primarily benevolent to primarily hostile, it follows that a propensity towards dis-ease (illness) becomes inevitable.

Chronic stress can significantly affect many of the body's immune systems, as can an individual’s perceptions of, and reactions to, stress. Immune system changes can create more vulnerability to infection. (Tsigos C, Chrousos G.P. Hypothalamic-pituitary-adrenal axis, neuroendocrine factors, and stress. *Journal of Psychosomatic Research*, 2002. 53, 865-871., Glavas MM, Weinberg J. Stress, Alcohol Consumption, and the Hypothalamic-Pituitary-Adrenal Axis in Yehuda S, Mostofsky DI. *Nutrients, Stress, and Medical Disorders*. 2006. Totowa, NJ: Humana Press. pp. 165–183.)

Chronic stress obliterates its short term positive physiological and mental benefits.

That which remains only displays its destructive capacity.