Stress and cerebral metabolism.

Stress or General Adaptation Syndrome (GAS) - set of adaptive responses a living organism generates as a reaction to an external stimulus. Stimuli such as a chemical or biological agent, environmental condition, and physical stimulus or an event that causes General Adaptation Syndrome is called stressor. A sickness, trauma, physical or mental straining, emotional shock, etc. could be a stressor.

The fundamental research on stress was accomplished by Hans Selye, Ph.D in Université De Montréal (1960). Dr. Selye has defined three stages of stress response:

1) Alarm.
2) Resistance.
3) Exhaustion.

Dr. Selye has also described the hypothalamic-pituitary-adrenal axis (HPA axis), a major part of endocrine system, that controls reaction to stress causing major hormonal changes in the body.

At the first, alarm stage, the body is alarmed by the stressors and generates an anti-stress response to reduce the stress. During prolonged or severe stress, the body cannot cope with the stress and stress hormone (cortisol) production starts to decline. Finally, the body cannot produce adequate amount of stress hormones and its stress-response abilities drastically decline.

If we look at the stress response sequence in grater details, we will see that under the stress, the medulla of adrenal glands and some neurons of the central nervous system (CNS) secrete adrenaline as a part of fight-or-fight response. Activity of noradrenergetic system is also increasing. Adrenaline and noradrenaline secreted by adrenals' medulla and CNS generally cannot permeate through brain-blood barrier (BBB). However, it is possible at certain areas of BBB, so called circumventricular areas. Adrenaline and noradrenaline stimulate the limbic-reticular system, particularly brain cortex and amygdale. As a result the HPA axis is activated through a mediator nitrogen-oxide (NO). Paraventricular nucleus of hypothalamus secretes corticotrophin-releasing factor that causes the pituitary gland to release of adrenocorticotropic hormone (ACTH). The ACTH stimulates production of glucocorticoids in the adrenal cortex. These hormones, particularly cortisol, stimulate neurons of the hippocampus. The hippocampus, in its turn, slows down the HPA activity by providing negative feedback.

Stress hormones cause various changes in the body: adrenal glands hypertrophy, thymolysis, involution of lymph nodes, inflammation response reduction, and changes in the functional state of central nervous system. (Detailed description of these processes is out of scope of this article. In this article, we analyze metabolic issues of this process.)

Adaptation to stress is achieved through changes in metabolism. Adrenaline causes hyperglycemia and slows down insulin secretion. The reduction of insulin concentration happens due to antilipolytic effect. The reduction increases lypolysis (under influence of lypolyc stress horomones). As a result, the body's demand for energy is satisfied by non-esterified fatty acids. Even in the brain, the break-down products of such fatty acids (called ketone bodies) used as a source of energy besides glucose. Cortisol also stimulates gluconeogenesis breaking down amino acids (catabolic properties of cortisol). Blood pressure also increases as a stress response reaction due to activation of sympathetic nervous system. The increased blood pressure will increase blood circulation in the body.

The functional state of the brain and its metabolism will change under stress. Positron Emitting Tomography (PET) shows increased blood circulation in certain areas of the brain, for example, in the frontal lobes. Stress hormones, glucocorticoids increase brain sensitivity up to seizure threshold reduction. The activity of the glutamatergic neurons in hippocampus increases under stress. This happens partially due to the glucocorticoids because such activity is reduced in lab animals whose adrenal glands were removed. Glutamate is an excitatory mediator whose role is important for memory functions. However, in higher concentration glutamate acts as neurotoxin due to excessive stimulation NMDA receptors, increase in-cell calcium storage and activation of calcium dependent phospholipase, protease, and endonuclease. Under the influence of the above-mentioned enzymes, the neuron structures degrade causing death of neurons. Neurotoxic properties of glutamate increase as concentration of the glucocorticoids rises. High concentration of glucocoticoids starts programmed death mechanism in the brain cells - apoptosis.

Glycolysis becomes dominant in the metabolism under stress. As it was mentioned ealier, under stress the brain also uses ketone bodies as a source of energy. This, along with glycolysis, leads to increased concentration of acidic products of metabolic breakdown in the brain. This process is called acidosis.

The decrement of in-cell pH disrupts the mitochondria breathing process incrementing free-radical oxidation processes. The acidosis also increases in-cell concentration of calcium contributing to apoptosis.

Changes in DC-potentials (DC-Shifts) in the brain under stress in alert state (waiting for a stressful event).

In this research, DC-potentials of mine-rescue team members were compared to those of a group of construction workers. The rescue team deals with mine accidents. Such work is associated with high stress level. The members of the second group are construction workers and do not deal with high stress in day-to-day work.

The salient feature of the rescue team is the waiting-for-the-alarm state, a demand to switch from a safe state to work that requires high concentration, is demanding and dangerous. Continuous waiting for an emergency to happen causes stress to develop.

The rescue team members had elevated DC-potentials in all the mono-polar channels (each channel has one sensor to measure the DC potential). They also have elevated average DC-potential.

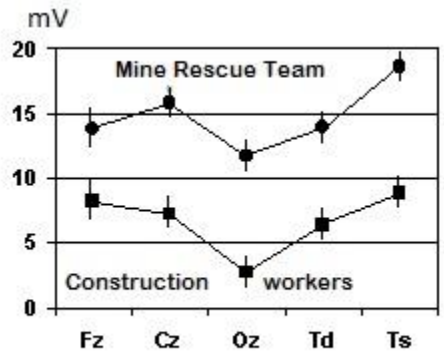

Figure 1. DC-potentials in mine-rescue group members and construction workers.

Fz – forehead;
Cz – vertex;
Oz – backhead;
Td – right temple;
Ts – left temple;

As it was explained earlier, the cerebral metabolism, blood circulation, glycolysis, and other metabolic processes increase under stress. These processes cause accumulation of the acidic metabolic breakdown products that lead to elevation of DC-potentials in all brain areas except the frontal lobes. This proves that metabolism increase and pH decrease in most areas of the brain under stress.

Similar DC-potential changes could be seen in people waiting for a surgery, even for simple, non-life threatening conditions. The worries preceding the surgery cause the stress response. During this time, the bio-chemical processes, electrical activity in the brain, number of psycho-physiological characteristics change in the body. All the changes in metabolic processes in the brain are caused by the HPA axis activation.

DC-potential deviations in the patients with pre-surgery stress conditions are comparable with those DC-potential deviations that could be observed in mine-rescue team members on duty. These deviations refer to the same changes in the cerebral metabolism that cause increase in brain acidity caused by various type of stress.

Connection between the brain DC-potentials and cortisol levels.

In order to find cause of DC-potential changes in the human under stress, a study was conducted to find connection between DC-potential and cortisol level in human. The study was conducted on 19 healthy elderly people of both genders (15 females, 4 males; 63±4.1 years old). DC-potentials were registered in the morning. Before the DC-potentials were measured, blood samples were collected for cortisol testing. The radioimmunological method was used to define cortisol level in the serum. The cortisol content was 451 ± 55.3 nmol/ with no distinction male/female. There was also no correlation observed between cortisol content and vegetative parameters such as: blood pressure, pulse rate, and Kerdo index.

Patients with higher cortisol levels had stressful situation in the past such as: death of relatives, divorce, etc.

DC-potentials were higher in frontal lobes, the right temporal lobe, and occipital areas in people with higher cortisol level. The average DC-potentials (averaged over all the channels) was also higher in people with higher cortisol level.

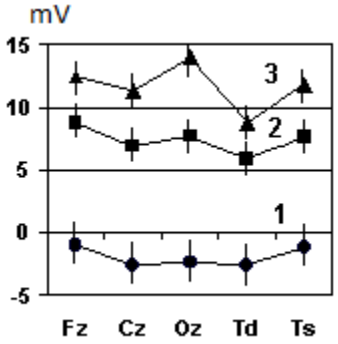

Figure 2. DC-potentials in healthy elderly people with low (1), average (2), and high (3) levels of cortisol in the serum.

Acquired data confirm that higher cortisol levels activate the HPA axis and increase levels of DC-potentials. This happens due to cerebral metabolism that leads to increased glycolysis and lactic acidosis.

Acquired data shows that HPA axis activation, increase cortisol levels are followed up by changes in DC-potentials. The changes in cerebral metabolism leading to increase in glycolysis and speed of brain acidosis development could be traced by changes in DC-potentials. The brain acidosis increases oxidative processes that are harmful for brain functionalities especially in elderly people.

Adaptation processes start in the body as a stress response. Such processes in first place mobilize energy resources. Glucocorticoids released as a result of the HPA axis activation, together with cathecholamines, open additional metabolic ways. In the

brain, blood circulation increases, also increases aerobic glucose oxidation, and glicolysis that also uses ketone bodies besides glucose. These processes cause acidification in nervous tissues and reduce blood circulation in the brain. DC-potentials change due to acidification of the brain in people under stress independently of stressor types.

Hyperventilation, for example, is also a stressor and followed by increase in DC-potentials. People under stress usually have dominating sympathetic nervous system. The connection between DC-potentials and Kerdo index shows involvement of the frontal brain lobes in vegetative regulation.

As it was mentioned earlier, stress starts adaptation processes in the human body, however, on the other hand, can cause detrimental consequences. Prolong acidosis is dangerous for neurons because low pH slows down respiratory processes in mitochondrial chains that increases formation of free oxygen radicals. The oxidative stress also increases calcium propagation into neurons. Calcium activates enzymes that cause degradation of cell structures. Prolonged acidosis leads to apoptosis – the process of programmed cell death.

Application of the DC-potential method allows controlling change in the acid-alkaline balance that could be used to observe and prevent negative influence of stress on the brain.

Abnormally high brain activity under stress is a sign of neurophysical instability, which could indicate cerebral pathology. Studying patients' DC-potential variations during hyperventilation, making the patients to take mnestic (memory) tests could also be used as a diagnostic tool for diseases with such symptoms as: lowering the threshold of convulsive readiness and atrophic processes.

The close connection between brain activities and changes in brain metabolism under stress allows using PET, fMRI and other methods for functional brain mapping. The method that traces changes in DC-potentals can also be used for functional brain mapping.