Lecture 11

STRESS AND GAS ROLE IN PATHOLOGY

Conception of stress was introduced into medicine by Canadian physiologist Hans Selye in the year 1936, and as we are known he borrowed this term from the mechanical sciences. Under this terminology he minded a pressure of different extreme factors to an organism These factors can be either of external or internal origin, infectious or non-infectious nature; for example, intensive surgery including massive blood loss, mechanical or barotrauma, burn, severe infection, autoimmune disease, and malignant tumors. Stress may be acute or chronic, and even of psychological nature.

Definition: it is a non-specific complex of psycho-physiological reactions of organism as a response to the life-threatening factors.

Experimental study of stress

In process of research of stress on the animals (white rats) Selye came to the conclusion that stress passed through three stages. The first stage was called him as alarm reaction, and it usually lasted for 24 - 48 hours. At this stage all reserved defensive possibilities of an organism usually become mobilized to struggle against a pathogen. The next second step named the phase of resistance when due to the long-standing compensatory mechanisms, very steady, an organism becomes adapted to stress and copes with the pathogen for enough a long time. In this case we say about a favourable course of stress. The third stage named the exhausting and its name can explain everything. The conversion of resistance stage into exhausting one is associated with an insufficiency of adaptive mechanisms to oppose a pathogen and destructive processes in the organism, provoked by stressor. The stage is very danger and may lead to a death.

Analyzing the different tissues and organs of the experimental animals under stress provoked multiple pathogens(formalin injection, exposition of the animals to loud sound or immobile condition during 24 hours), Selye came to conclusion that non-specific triads of the symptoms was very characteristic of the stress. The triad described by Selye consists of:

- -hypertrophy of the adrenal cortex
- thymic gland and lymph nodes involution
- -in 30%-40% of cases there were the ulcerative processes in the gastrointestinal tract.

Selye described morphologic and functional changes in adrenal gland of the rats, endured stress, according to three stress stages. At the first stage adrenal cortex was very rich of the secretion granules with their high activity, accompanied by an excessive cortisol production. At the second stage there was a very steady hypertrophy and hyperplasia of the adrenal cortex, those were provided by the lot of mitosis in this area, naturally, with increased cortisol secretion. But at the third stage an adrenal cortex became very thin and exhausted of secretion granules. Clinically it sounds that stress seems to be is one of the reasons of an acute adrenal insufficiency. It must be added, that study of Selye came us to an idea of replacement treatment of patients with short-termed, high doses of cortisol in case

of extreme situation, associated with severe stress. Besides, excess of cortisol in stress also can explain an involution of thymus and lymph nodes as a variant of immuno-suppression. Such cortisol ability get used in the hypersensitivity conditions treatment. But cortisol in a large dose may provoke the ulcers in gastrointestinal tract. So, according to Selye's observations, stress seems to be the condition of hypercortisolism which possesses by double meaning, positive and negative.

General adaptation syndrome (GAS)

The term GAS introduced by Selye minds a non-specific reaction of whole organism to the stress situation. Now we consider it as a part of an acute phase response, however, GAS seems to be the only the part of an acute phase response when hypothalamo-pituitary-adrenal glands system plays a pivotal role. There is no doubtful, that Selye didn't study precisely the behavior of immune and hematopoietic systems during the GAS, but hypothalamo-pituitaty-adrenal axis activation precisely was in his field of view. GAS seems to be only a neuroendocrine part of an acute phase response. It must be added, that in difference to acute phase, response, GAS can be provoked not only by infectious and noninfectious factors (material substunses) but psychological factors too, moreover, we can single out a psychological stress.

The ways of GAS realizing may be represented by the following chain of the events:

- *Stressors activate different receptors of an organism: exteroreceptors – nociceptors which are found in the skin, mucosal lines, interoreceptors in the blood vessels wall, and sleeping nociceptors in the internal organs, moreover, analyzers, such as visual and hearing receptors
- Next step is activation of monoaminergic neurons in CNS which control the peptidergic neurons of hypothalamus. It mast be added, that monoaminoergic mediators include such very important neurotransmitters as catecholamines, serotonin and GABA. They are responsible for a balance between releasing and statin- factors secreting by the hypothalamus
- CRF, in turn, stimulates elaboration and secretion of ACTH by basophil cells of the pituitary gland
- The last event in described above chain is synthesizing and release of glucocorticoids by the adrenal cortex

All these events are accompanied by high level of blood catecholamines, secreting by the sympathetic endings of corresponding fibres, adrenal medulla, and other variants of chromaffin tissue sources. Such reactions result in flooding of the blood with catecholamines and glucocorticoids

So, the stress axis, according to Selye's theory, may be represented in form of the following sequence of the events depicted below:

Hypothalamo-pituitary-adrenal gland axis activation as a base of stress-reaction

Stressor influence the different receptors including analyzers

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Activation of monoaminergic synapses in CNS

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Hypothalamus activation and CRF secretion

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Secretion of ACTH by pituitary gland

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Increase of synthesis and production of glucocorticoids by adrenal cortex

It is not doubt that sympathetic nerve system plays role of an initiator in stress reaction, but at the same time, the response in form of high cortisol production supports and prolongs the endocrine pattern of GAS.

Hence, we have two major hormones of stress, catecholamines and glucocorticoids. However, effects of catecholamines is shorter in comparison with glucocorticoid ones. The lasts can support a long- standing adaptation of an organism to stress because, on the one hand, glucocorticoids enhance and prolong sympathetic nerve system effects but, on the other hand, high level of blood glucose is maintained not only by the catecholamines but by such effect of cortisol as gluconeogenesis. Both activate lypolisis for energetic needs and, eventually, catecholamines accelerate systemic blood flow. Nowadays, serious surgery with postoperative trauma, burns, massive blood loss and accident of bronchial asthma in form of status asthmaticus need the glucocorticoids for treatment. It is forced to life safe measures in form of hormonal replacement of failed cortex glucocorticoid function during a stress.

Protective role of stress hormones

Catecholamines

At the start of XX century French physiologist Claude Bernard, studying the level of blood catecholamines in the animals under life critical situations, signed them as the hormones of the ”fight and fly.”

These hormones can help not only the animals but the man too to overcome physical and psychical extreme situations. Being the first line of a defense in these life-threatening conditions, catecholamines mobilize all reserves of an organism. They possess by positive physiological and psychological effects. On the one hand, these hormones influence positively the metabolism of tissue and organs but, on the other hand, activate psychical abilities, and such way they postulate an appropriate behavior to organism surviving in extreme situation.

What are the mechanisms of defensive influence of catecholamines during a stress?

1. Support a proper level of glucose in the blood via activation of glycogenolysis in the liver.

Fat tissue is one of the most important target to catecholamines, and via beta-1 adrenoreceptors they activate lipolysis when free fatty acids can be used as a high energetic substances. It is especially important for a supporting of the heart and strip muscle activity during “the fight and fly”

2. Influence the cardiovascular system. Possessing by positive chronotropic and ionotropic effects, they correspondingly promote tachycardia and increase in a heart stroke volume, and, such way, increase minute cardiac volume. This, in turn, results in adequate organs blood perfusion when metabolic request is higher than in

normal. They also maintain an appropriate arterial pressure, both systolic and diastolic

3. Redistribution of the blood flow in use of the most life-important organs (brain and heart) is a function of the catecholamines too. Via activation of alpha receptors of the small vessels of the peripheral organs they drive the blood into central organs and increase end- diastolic presser in the heart that, in turn, increases heart stroke volume. Moreover, via beta-adrenoreceptors epinephrine dilates the brain and coronary heart vessels which so necessary for their high activity.

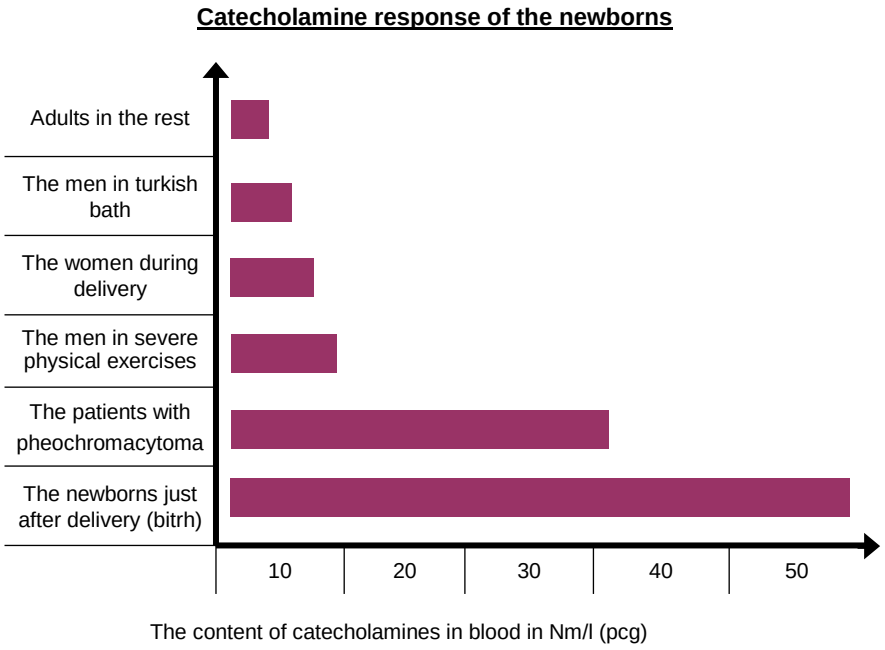
4. Increase in rate and depth of breathing to support an organism with oxygen supplying.

5. Mobilize a psychical activity to rational behavior and avoiding of the mistakes in that not easy to organism situation.

Catecholamine adaptation of the newborns, altering their delivery is the bright example of positive influence these hormones a stress- reaction.

Possible causes of their stress may be evoked by an inevitable hypoxia under which newborns have occurred with during the passing through the delivery ways. However, the pediatricians believe the stress is useful for the newborns due to a very high level of the blood protective catecholamines in their organism that time.

Comparison of the analyses of blood catecholamine content in the newborns with the men content during physical exercises, in sauna and in women during delivery, moreover, in a patient with pheochromacytoma (benign tumor arised from adrenal medulla and producing cathecholamines)) revealed that the most concentration of these hormones is really in the blood of the newborns. The catecholamines protect the newborns, make them more adaptive to the new life. It was estimated that the children born “per vias naturalis” are more resistant to possible unfavourable life conditions than those, who beared by Caesar’s section. Protective effects, except described above, includes reabsorbtion of the water from the surface of the lung just after delivery and synthesizing of surfoctant which decreases surface tension in alveoles to avoid of their collapse in respiration.



Picture 9. Catecholamine response of the newborns in comparison with the same of other groups of people

Besides, activation of sympathetic nerve system results in dilation of the pupils, and possibly, takes part in initial sense attachment (love) between mother and her child. According to the photos of the newborn's faces they looked happy when enter our world.

Glucocorticoids

They provide long-termed protection of an organism against the pathogens and unfavourable consequences associated with provoked by them organism destruction. Positive role of glucocorticoids may be illustrated by the following effects to the metabolism and their influence some organs and tissues:

- Like cathecholamines they maintain blood glucose but via active gluconeogenesis and lipolysis
- Support proper blood circulation, acting as permissive substances in relation to the catecholamines
- They are considered as indirect modulators of CNS functions, because a high concentration of glucocorticoids is a result of active secretion of CRF. At the same time, our behavior and, moreover, our immunity depend on the production of CRF by the hypothalamus.

Anti-inflammatory properties of glucocoricoids

Glucocorticoids inhibit release and production of pro-inflammatory mediators via suppression of an activity of different membrane phospholipases. This effect is associated with synthesis of protein lipocortin by the cells in the site of inflammation. Such mediators as histamine, derivates of arachidonic acids, PAF, and different intracellular hydrolases are responsible for multiple phenomena of inflammation. Among them are increased permeability, activation of microcirculation, leukocyte emigration and chemotaxis; in any case become

evident that inhibition of their activity is equal to anti-inflammatory effects. In addition must be said that glucocorticoids can inhibit an immune response, especially, cellular, and such way act as immunosuppressive substances.
The most important shifts in blood cell population under glucocorticoids
During a stress the following hematological indices usually observed: leukocytosis with absolute neutrophilia and regenerative left shift of neutrophil nucleus, but lymphopenia and eosinopenia. Glucocorticoids seem to be the cytoclones to the neutrophils but, at the same time, they redistribute and destroy the lymphocytes decreasing in their quantity.

Stress-limiting systems and their role in a stress reaction

As was described above, stress triggers activation of sympathetic nerve system which, in turn, leads to hypersecretion of ACTH and cortisol. But non-limited catecholamine effects may result in overwhelming destruction of various systems and organs, and go an organism to the ruin. In prolong time of biological evolution some stress-limiting system were developed to protect an organism against its destruction. These systems via their corresponding mediators can limit both, central and peripheral exceed responses to the stress factors.
Among them, the most important are the central opioid, serotonin and GABA systems. It seems they realize a training of any organism to repeated insults that occur in normal too, but at the same time stress-limiting reactions become more active in GAS. As for peripheral stress-limiting system, anti-oxidant, prostaglandin and adenine- nucleotides ones may be mentioned. But the central mechanisms are the most important for limiting very stormy effects of the catecholamines. The opiate system become involved in a classical response to the stress and realized due to such opioid peptides as endorphins and enkephalins. It must be said that both, ACTH and beta-endorphins have the same source in form of propiomelanocortin which is synthesized in the pituitary gland. However, during the stress they are produced simultaneously in a very high concentration. The other opioid peptides of this family are synthesized in the multiple regions of the brain and by the adrenal medulla enterochromaffin cells.

Effects of opioid peptides

They increase a threshold of pain sensitivity of the nociceptive receptors and such way inhibit a sense of pain during the stress. This, in turn, helps an organism to concentrate all physical and psychical reactions (severe pain restricts these possibilities). The mechanism of pain inhibition is the following: beta-enkephalins play the role of neurotransmitters which are working in serotoninergic antinociceptive system, where they suppress release of substance P by the presynaptic terminates in the secondary neurons, situated in the posterior horns of the spinal cords. The conduction of pain through the secondary nociceptive neurons is inhibited or suppressed completely.
Suppressed activity of sympathetic nerves system under opiates seems to be a result of restriction of catecholamines release by specific presynaptic terminates or catecholamines influence the postsynaptic nerve endings in corresponding synapses. Taking in mind a very important triggering effect of sympathetic nerve

system in stress, it's become possible to understand an anti-stressor effect of the opiates.

The next stress-limiting system is serotoninergic. During a stress elaboration of serotonin in CNS, especially, in locus coeruleus and in the regions closely related to limbic system is increased. Undoubtedly, that serotonin influences the behavior of the man realized not only for a stress. However, during the stress, when concentration of serotonin in the blood extremely high, activation of descending anti-nociceptive central pathways and associated with it modulation of the behavior, may help the people to pass through the unfavourable stress situation, especially when it is acute stress.

Moreover, stress-reaction which can be provoked by different factors is accompanied by GABA-system activation. In experiments on the animals GABA-system stimulation inhibited an appearance of stomach ulcer, heart fibrillations, and arrest of an extreme heart activity as the examples stress negative consequences.

All in all, analyzing stress-limiting reactions must be said that glucocorticoids, themselves, are an important line of defense during the stress. Except mobilization of our energetic resources, glucocorticoids possess by strong anti-inflammatory properties, moreover, via immunologic mechanisms they can eliminate foreign tissue substances which can support inflammation. Cortisol inhibits both, release of preformed mediators of inflammation and their synthesis "de novo", including acute phase response cytokines, besides, it seems to be not a very strong but an immunosuppressor.

From stress to the disease

This problem is closely associated with the targets which "are chosen" by stress to injury. It may be supposed some factors which the certain diseases depend on. Among them are the following conditions:

- Genetic predisposition (age, sex, etc) of an organ which is involved
- Intrinsic factors, such as nutrition, possible infection, and psychical condition of an organism at that moment
- Frequency and heaviness of the stress factor action to chosen organ

Nowadays, a very popular the theory of hypokinesia according that lack of physical activity and prolong internal organ's hypofunction may lead to a disease.

Next is, so named, psychosomatic diseases. By psychosomatic disease we call pathology when the start and basic mechanisms of primary disturbances underlie in a psychic (psycho-) but, secondary, concerns with a special organ (somatic).

Now as psychosomatic diseases we mind the following: ischemic heart disease and its life-threatening complication as myocardial infarction, hypertonic disease, and stomach ulcer. Other diseases, for example, neurodermatitis, migrene in form of hemicrania are under our suspicion too. Sometimes, they are named as the diseases of adaptation but rather, according to Hans Selye, they are diseases of crashed adaptation.

Stress and cardiovascular diseases

Cardiovascular system is the main target to stress factors. The patients with ischemic heart disease and essential hypertension are very sensitive to the strong emotions due to a high level of genetic responsiveness of the adrenoreceptors. At the same time, very often such responses are accompanied by activation of the heart and small vessels functions. It needs a lot of catecholamines and correspondingly of cortisol. The hectic function of these organs constantly is under prolonged activation of stressor axis. It leads to periodically or for a long time to flooding an organism with catecholamines and glucocorticois. However, during a long stress-reaction adrenal cortex becomes exhausted. Moreover, sometimes, adaptive mechanisms, being prolonged and excessive, turn into disadaptive, and it is a real way to pathology.

There is the lot of evidences which support this theory. Analysis of the family history of patients with myocardium infarction, severe arrythmias and hypertonic disease revealed a connection of disease with a stress. It must be said that more often the disease usually occurred in some months later an insult. It is necessary to list the basic pathogenetic features which supposed to be were involved in .

The role of the stress in pathogenesis of hypertensive conditions

There are the following neurohumoral factors are suspected:

- Vasoconstrictive effect of catecholamines
- Periodicaly exitation of the baroreceptors of sinocarotid and aortal zones under stress leads to growing of their base tone; the receptors become accustomed to abnormal high arterial pressure (for this reason a patient doesn't have unpleasant sense). As a result, baroreceptors begin to accept increased blood pressure as a normal one. So, prolong activation of sympathetic nerve system in stress an organism needs the higher figures of AP in comparison with normal
- Increased level of blood cortisol possesses by permissive influence the sympathetic tone on the one hand, but on the other hand, in a high dose glucocorticoids act like mineralocorticoid aldosteron ; the last retains sodium in the blood, and such way increases ECFV (extracellular flow volume)
- Activation of RAAS via direct sympathetic effect to kidney blood flow leads not only to increase blood circulation volume but increases peripheral blood vessels resistance

Stress, ischemic heart disease and myocardial infarction

Together with hereditary factors, smoking, hypo-adynamia and overweight stress is the one of the most important among the risk factors. The following pathogenetic factors seem to be involved in these diseases outstanding:

Prolong coronarospasm under increased blood level of the catecholamines with the following ischemic injury

- Increased level of intracytoplasmic myocardiocyte Ca^{++} and its results:
- a.activation of different membrane phospholipases in cardiomyocytes with increased lipid peroxidation

- c. derives of arachidonic acid formation with prostaglandines and leukotriens negative pro-inflammatory effects
- d weakness of CPR activity and accumulation of Ca++ in cytoplasm of cardiomyocytes
- e. weakness of energy elaboration due to overload of mitochondria with Ca++

All listed above factors lead to disturbances in systolic and diastolic function of the heart and myocardium insufficiency.

Catecholaminemia, in turn, activates coagulation system and such way increases risk of thrombi formation in coronary arteries. Redistribution of the blood flow during a stress diminishes perfusion of the heart. Stimulation of sympathetic nerve system may provoke different types of arrythmias which negatively influence the coronary flow. It can be explained by significantly decreased time of diastole, but coronary perfusion realizes namely that time.

Stress is associated with lipolysis, but hyperlipidemia is one of the most important factors of atherosclerosis formation, including coronary artery atherosclerosis.

Role of stress in stomach ulcer formation

Stress is one of the risk factors which responsible for the ulcers in gastrointestinal tract together with hereditary factors and abnormality in patient's diet. Stress encourages an activation of both, sympathetic and parasympathetic nervous system. Their high activity may lead to imbalance in stomach glands secretion which can result in production of very aggressive gastric juice with possible peptic ulcer formation as autodigestion. Simultaneously, catecholamines may provoke spasm of the vessels, supplying the stomach. Ischemia and ischemic injury with a deep defect in the stomach wall seem to be the unfavourable consequenses of these processes. It must be added, that hypercortisolism which accompanies stress, plays a "vicious "role in this case. First of all, glucocorticoids enhance the protein catabolism and such way retard a regeneration of the epithelium of gastrointestinal tract, weakening the connective junctions between the epithelial cells. Lasts let the protons, secreting by the parietal stomach cells to be reinfused and injury a stomach wall.

Glucocorticoids increase stomach juice secretion but depress mucose, bicarbonates and prostaglandins production, and such way they decrease protective mechanisms that in normal, in sum, form gastroprotection against the different insults. It must be added, that prostaglandins influence positively the local blood flow and mucose plays role a mechanical barrier. Besides, mucose contents the factors of immune protection (IgA, T-lymphocytes) and, eventually, bicarbonates that diminish an acidity of stomach juice. In a resume must be said that stress provokes an injury of stomach wall but, at the same time, weakens the forces that it watching and surviving.