Materials of the Conferences

HORMONE-ADAPTIVE-METABOLIC MODEL OF CHRONIC NON-INFECTIOUS DISEASE FORMATION – NEW CONCEPT OF PREVENTIVE MEDICINE

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An original strategy of chronic non-infectious human diseases treatment and prophylaxis, in the basis of which the model of hormone-adaptive-metabolic imbalance lies, is offered.

With the body's stopping growing and developing the factors which provide them (somatotropic hormone and others) don't disappear but keep on having effect with a specific constancy causing inhibitory effects of glucose and amino-acids transportation through cells' and vascular membranes. This leads to chronic energy failure which can be qualified as substrate hypoergosis. Hypoergosis is the basic factor which forms chronic non-infectious diseases (atherosclerosis, hypertensive disease, diabetes of the II type and others) by means of mechanisms of hormone-adaptive-metabolic misbalance. Possible nosotropic mechanisms of main human chronic non-infectious disease genesis and principles of their treatment and prevention are shown forth here detailed enough.

The epidemiologic situation fully formed over recent years in the Russian Federation which is connected with the growth of cardiovascular diseases and considerable increase of death rate because of them represents a direct health risk for the population and the losses inflicted result in significant economic disbenefit. The economic disbenefit conditioned by temporary or constant loss of earning capacity, untimely death because of hypertension complications, ischemic heart disease and cerebrovascular diseases, only in 1999 made about 29,3 billion roubles, and by 2005 it had increased by an order greater.

The world's experience points at present abilities of increasing human and material losses because of the specified diseases; one of them serving as primary and secondary prevention measures, which represent a promising area of health care. As the theoretic foundation of preventive measures all over the globe now the concept of disease development risk factors stands out. The success of this concept application which is the framework of "the second antiepidemic revolution" (screening – examination with risk groups revelation) is definite. In many economically developed countries the morbidity and death rates because of cardiovascular diseases have decreased. However, the appearance of risk factors themselves inaugurates the developed pathologic process which so far has not taken the form of a specific nosologic disease. This complicates carrying out primary preventive measures of chronic somatic diseases. It should be also taken into account that the correction of high risk of chronic somatic disease development more often than not calls for the necessity of pharmacologic preparations use. First, it is unlikely to be efficient in the population level, and second, from the carried out research of such countries as Sweden and the USA it is seen that present-day therapeutic agents have no affects on chronic non-infectious disease death rate [1,2].

Thus, it appears to be of current interest to form a new conceptual avoidance and treatment policy that would allow preventing not only the risk of somatic pathology development, but also, in the conditions of the developed pathology, planning methods and principles of chronic non-infectious disease medical rehabilitation pathogenetically wisely.

By now certain scientific data in various fields of medical knowledge which are the precondition for creating a new strategy of prevention and treatment of chronic non-infectious diseases, that is: the ontogenetic medicine model of Dilman V.M. [4], the hypoergosis notion formulated by Yefuni S.N., Shpektor V.A. [5] and the stress theory of Selye G. [11], have been cumulated.

The basic thesis of the ontogenetic model is the statement about the fact that the main non-infectious human diseases are formed in ontogenesis under the effect of growth and development factors (somatotropic hormone, placental lactogen and others) which don't disappear with their finishing, but affect with a specific constancy. By now it has been known

that a somatotropic hormone (STH) possesses an acute insulinoid and chronic contrinsular effects [6]. That is why it is not difficult to suppose that even in a healthy organism under the effect of STH with the course of time inhibitory mechanisms of partial limitation of glucose uptake by the cells and tissues of an organism are formed, in other words – a diabetogenic state comes into being. The presence of diabetes of the II type in acromegaly patients confirms this fact. However, in 1981 Yefuni S.N. and Shpector V.A. offered to bring the term "hypoergosis" [5], having subdivided it into hypoxic, enzymatic and substratic ones, into the classification of hypoxias. In the opinion of the denoted authors, an energy failure of cells and tissues of the organism lies in the basis of hypoergosis. The substratic hypoergosis conditioned by the lack of substrate in the cell can realize the three main pathogenetic directions of human chronic non-infectious diseases:

1) Citric acid cycle, glycolysis, gluconoegenesis in all live systems, as a rule, are in the costate; the energy system of the cell being defined by the correlation of nucleotides – adenosinediphosphate – adenosinetriphosphate – adenosinemonophosphate (ADP-ATP-AMP) [7]. In case of ATR synthesis on any of the reasons (lack of substrate, oxygen or enzyme), and as a result, its decreasing in the cell, a disequilibrium of the cell's energy system towards ADP increase, that leads to the glycolysis key enzyme – phosphofructokinase, activation. This enables to keep up a sufficient cells' energy potential, but only on account of the glycolysis system. The provider of energy substrates for the glycolysis is a gluconeogenesis. A by-effect of the glycolysis is lactate accumulation – lactacidosis. From now forth, with decreasing of acetyl coenzyme A (CoA) derivative, in the Krebs cycle its accumulation takes place which leads to the synthesis of β-oxy-β-methylglutaryl-coenzyme-A (OMG-CoA) from the three CoA molecules. The OMG-CoA is converted into mevalonic acid which is a cholesterol precursor. From the mode of the OMG-CoA formation the reaction can go either towards cholesterol synthesis or towards ketone bodies formation. Ketoacidosis appears, i.e. β-oxidation of aliphatic acids in the liver activates, and fatty energy way starts prevailing. Gluconeogenesis supposes albuminolysis as well. The immune system albumin, being the most mobile one, splits at that causing immuneogenesis changes [4]. The inhibitory mechanisms of partial limitation of glucose uptake, which initiate the formation of substrate hypoergosis, stimulate hyperglycemia and hyperinsulinemia, that activates cholesterol, triglycerides and lipoproteides synthesis in the liver. The activation of β-oxidation of aliphatic acids and intensification of cholesterol synthesis out of mevalonic acid as well as the direct mobilizing effect of somatotropic hormone on the lipolysis lead to lipid accumulation in the immune system cells, that results in the inhibition of cellular immunity and promotion of humoral one. The accumulation of lipids on thrombocytes leads to activation of thromboxane and exhaustion of prostacyclin [4];

2) Founding on the stress concept of Selye G. [11] a series of stereotyped adaptive reactions intended to provide the defence of the organism appears in vivo in response to any alterations requiring its working capability increase. The totality of these defence reactions got the name of "general adaptive syndrome", or "stress" for short, and the factors causing it were denoted as "stressors". The pathological processes appearing because of the stressors' action Selye G. denoted as adaptation diseases. Hypoxia is known to be one of the most powerful stressors. But as long as in the competence of Krebs cycle three interchangeable factors matter – adequate content of CoA, enzyme and O_2, the decrease or absence of one of these factors lead to the ATP synthesis disorder, that activates the nonspecific stress and adaptation mechanisms through hypothalamus, pituitary and adrenal cortex. That is why the lack of metabolic substrates (substrate hypoergosis) or enzymes (enzyme hypoergosis) can be referred to stressors quite as much as hypoxia, with the only difference – the first two factors affect mostly in delayed mode, i.e. chronically or subacutely, and hypoxia, most commonly, - acutely.

Thus, proceeding from the statement that hypoergosis being a powerful endogenic stressor naturally promotes the nonspecific "adaptive" brain and body system and gives rise to adaptation diseases within the frame of the general adaptive syndrome formation. This scheme can be introduced as follows: a powerful endogenic stressor – substrate or enzyme hypoergosis promotes releasing of – hypothalamic hormones which, in their turn, activate pituitary hormones (ACTH, STH, TTH

and others), and the last, in their turn, provokes the discharge of stress hormones (cortisol and mineralcorticoids). Therefore, the hypoergosis patient's body lives in the state of constant chronic stress. In the course of time it results in appearing of a pathologic state resembling "cushingoid" – fatty degeneration of face and the upper part of the body, disorders of hydro-electrolytic metabolism, emergence of hydrops, peripheric vessels spasm and arterial tension rise, secondary kidney ischemia with rennin-angiotonin-aldosterone system agitation;

3) Following the concept of Yefuni S.N. [5] about hypoergosis as a state when not a decrease, but vice versa – an increase of O_2 tension in the cell, i.e. hyperoxia, takes place, it is necessary to give consideration to this complex of hypoergosis pathogenesis mechanisms.

The cell hyperoxia provoking the processes of lipid peroxidation (LPO) appears as the result of a surplus content of O_2 in the cell because of its abated utilization. The formation of O_2 active forms, being more powerful oxidation agents than molecular oxygen, is one of the most important conditions for the LPO processes running [8,9,10]. The formation of O_2 active forms is the consequence of an incomplete single-electron ($O\cdot$), two-electron (H_2O_2) or three-electron ($\cdot OH$) electronation instead of the complete four-electron one resulting in water formation. The process of complete reduction of O_2 to H_2O is more energy dependent than the processes of incomplete reduction; that is why it becomes clear that the formation of O_2 active forms comes into being in particular with the deficit of energy substrates and finally – ATP. Hyperoxia not only initiates the processes of LPO, but also changes the DNA structure, damages collagen, hyaluronic acid, exhausts the antioxidant system, provokes the activation of arachidonic acid synthesis with the formation of prostaglandins, leukotrienes and interleukins [4,8,9,10].

These are the principle directions of pathogenetic mechanisms of main non-infectious diseases. However, with the formation of chronic diseases one can find both common features typical of this whole group of diseases, and specific features of pathogenesis characterizing a certain disease. For example, for atherosclerosis a typical and prevailing mechanism of pathogenesis is the cell hyperoxia with the formation of O_2 active forms which initiate the LPO processes on cells' membranes. It is the primary damage of the intima of arterial vessels and cells' membranes that underlies arteriosclerosis, and only then the process of atherosclerosis plaque deposits to the damaged vessels' intima associated with lipid metabolism disorder, nascence of immune lipid complexes conditioned by glycolysis and gluconeogenesis.

The pathogenesis of obese diabetes is more complicated. Chronic or subacute hypoergosis leads to hyperglycemia and hyperinsulinemia which, in the course of time, forms resistance to insulin receptors. This, early or late, results in the atrophy of β-cells of the pancreas. Being a powerful stressor, hypoergosis leads to activation of the adaptive system with the increased synthesis of contrinsular hormones which stimulate glycolysis and gluconeogenesis and, as the result, fatty energy way (β-oxidation of aliphatic acids) starts prevailing. Lactacidosis and ketoacidosis grow. Arteriosclerosis is in progress. The cell hyperoxia leads to micro- and macroangiopathies. Glycolysis and gluconeogenesis provoke immune disorders.

Arterial hypertension has more simple mechanisms of pathogenesis. Hypoergosis, being a powerful endogenic stressor, activates the adaptive system, leading to a chronic discharge of stress hormones which define the peripheric vascular effects, stimulate pressor albumin factors synthesis by a vascular wall (neuropeptide-Y, endotelines 1,2,3). Psycho-emotional factors (stressors) also have a definite significance.

In the basis of the ischemic heart disease appearing mechanisms also hypoergosis lies and it initiates the LPO products' and boosters' [8,9,10] membrane damaging action and is mediated by the following mechanisms:

1. By the LPO over activation conditioned by the cell hyperoxia when a considerable part of membrane phospholipids is subject to peroxidation degradation and lipid phase of the membrane becomes more rigid. It limits the conformation mobility of the polypeptide chain and, as the result, the capacity of enzymes, receptors and canal forming albumins built into the membranes, decreases. The formation of interlipid, interalbumin and lipid-albumin cross-links on account of cooperation with secondary LPO products and, in particular, with malonic dialdehyde, promotes it. Such course of events being attended, for example, by the inhibition of

sarcoplasmic reticulum Ca-ATPhase activity leads to failure of Ca^{2+} removal from sarcoplasm and realization of damaging action of this cation excess over cardiac myocytes [8,9,10];

2. The Ca^{2+} intracellular concentration increase promotes the intensity of this cation penetration into the cell from the ectocytic medium. It is connected with the fact that during the LPO process in the water-repellent "tail" of an aliphatic acid there appears a hydrophil peroxy group. If complexes of such oxygenized phospholipids in every of the membrane's monolayers turn out to be located one opposite the other, then canals of hyperpermeability (clusters), which are permeated, in particular, for Ca^{2+}, are formed.

The overincrease of such clusters' amount can become the foundation of fragmentation and destruction of the sarcolemma membrane and sarcoplasmic reticulum;

3. The appearance of a hydrophil peroxy groups' membrane lipid bilayer in the water-repellent area kind of "loosens" this area and makes the present in it albumin components more penetrable for proteolytic enzymes. It promotes the destruction of bio-membranes as well;

4. The direct oxidation of sulfhydryl groups in active enzyme centres, enzymes as well, located in membranes leads to the activation of these enzymes and the membranes' permeability increase;

5. The destruction of the substances possessing antioxidant activity (vitamins, steroids, ubihinon).

A very important conclusion follows the above said: thanks to the unbalanced LPO activation induced by free oxygen radicals, the plasmalemma, as well as the membranes of intracellular organelles – chondriosomas, sarcoplasmatic reticulum and lysosomas breakdown happens. It leads to the inhibition of oxidative phosphorylation and Ca^{2+} transportation, releasing lysosome autolytic enzymes, deep functional disturbance and, finally, nectrocytosis.

Thus, on the basis of the offered model – hormone-adaptive-metabolic imbalance of the body, it seems to be possible to state its fundamentals, and also the concept of the avoidance policy and treatment of human chronic non-infectious diseases.

1. In the root of human chronic non-infectious diseases emergence a substrate hypoergosis – a chronic energy deficiency of cells, systems and organs, lies.

2. The main etiologic factors initiating hypoergosis seem to be the factors of growth and development (STH, PL and others), in the result of chronic action of which inhibition mechanisms of partial glucose and amino acids transportation and utilization limitation.

3. STH, possessing chronic contrinsular action, performs conformation changes of cells' and vascular membranes, that leads to the breakdown of glucose and amino acids transportation and utilization, that, after all, results in the complex of compensatory- adaptive reactions of the body aimed at enhancement of its energetics.

4. A side product of compensatory-adaptive reactions of the body, aimed at its homeostasis restoration, i.e. a means of realization, is the body's homeostasis hormone-adaptive-metabolic imbalance leading to the accumulation of semi-oxygenated metabolic products.

5. As the result of the forming hormone-adaptive-metabolic imbalance of the body, the energy mode changes lawfully, stepping gradually from energetically beneficial aerobic oxidation of metabolic substrates to a less beneficial – anaerobic way of glucose oxidation, that leads to the accumulation of products of damaged metabolism and adaptation diseases formation.

6. The substrate hypoergosis is the main "basic" pathogenetic factor forming chronic energy deficiency in the body, and the manifestation of chronic non-infectious diseases, apparently, is realized both with the help of risk factors and with the help of various external "permitting" stress factors (smoking; alcohol overindulgence; adynamy; overconsumption of saturated fats, hydrocarbons, salt; psycho-emotional stress, chronic infection and others).

Methods and principles of treatment and prophylaxis of substrate hypoergosis are based on these statements; they including the following measures:

1. Appropriate motor regime, removing insulin resistance of cells' membrane receptor apparatus, which appeared against the background of adynamy and chronic action of STH.

2. Rational balanced diet with enough accessory food substances and antioxidants,

unsaturated fats, trace substances, dietary fiber, pectin, and other components.

3. Strict control of patients' weight, excluding risk factors.

4. Administration of individually tested medicaments from antioxidant and antihypoxant groups on the method of Foll R. in case of a pathological process manifestation.

5. Regulatory and traditional therapy (multiresonance and bioresonance therapy, homeopathy, reflex therapy, manual therapy, tripsis, phytotherapy, leech therapy, apitherapy, exercise therapy, respiratory gymnastics and other kinds of medical rehabilitation.

6. If necessary, a palliative care (disaggregants, vascular, neuroprotective, neurotrophic antihypertensive drugs and others).

The offered measures of prophylactic and rehabilitation actions should be carried out on the patients permanently, without intermission, because the main pathogenetic factor "substrate hypoergosis" functions in the human body chronically on constant conditions.

Thus, the offered concept can be a theoretic foundation for the realization of priority national projects in the field of human chronic non-infectious diseases prophylaxis and treatment. It will allow putting the principles of prophylactic and remedial treatment of atherosclerosis, hypertension disease, ischemic heart and brain disease, diabetes of the II type, metabolic immunosuppression, etc. into practice pathogenetically intelligently and highly effectively.

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EVALUATION OF THROMBOCYTE CAPACITY AS METHOD OF EARLY DIAGNOSTICS OF HEMORRHAGIC SYNDROME AT CRIMEAN-CONGO HEMORRHAGIC FEVER

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Nowadays in the Southern regions of Russia, as well as in Astrakhan Region, a steady incidence rate of Crimean-Congo hemorrhagic fever (CCHF) is marked (Maleyev V.V., Sannikova I.V., 2005); up to 9% of fatal cases of the disease being registered (Maleyev V.V., 2003), the root of which is in deep hemocoagulation disorders. According to the modern data, the initiating role in the pathogenesis of hemorrhagic syndrome and thrombotic complications at many infectious processes is played by thrombocytes (Polyakova A.M., 2000).

With the purpose of carrying out a modern and appropriate pharmacological correction of hemostasis disorders at CCHF there appeared a